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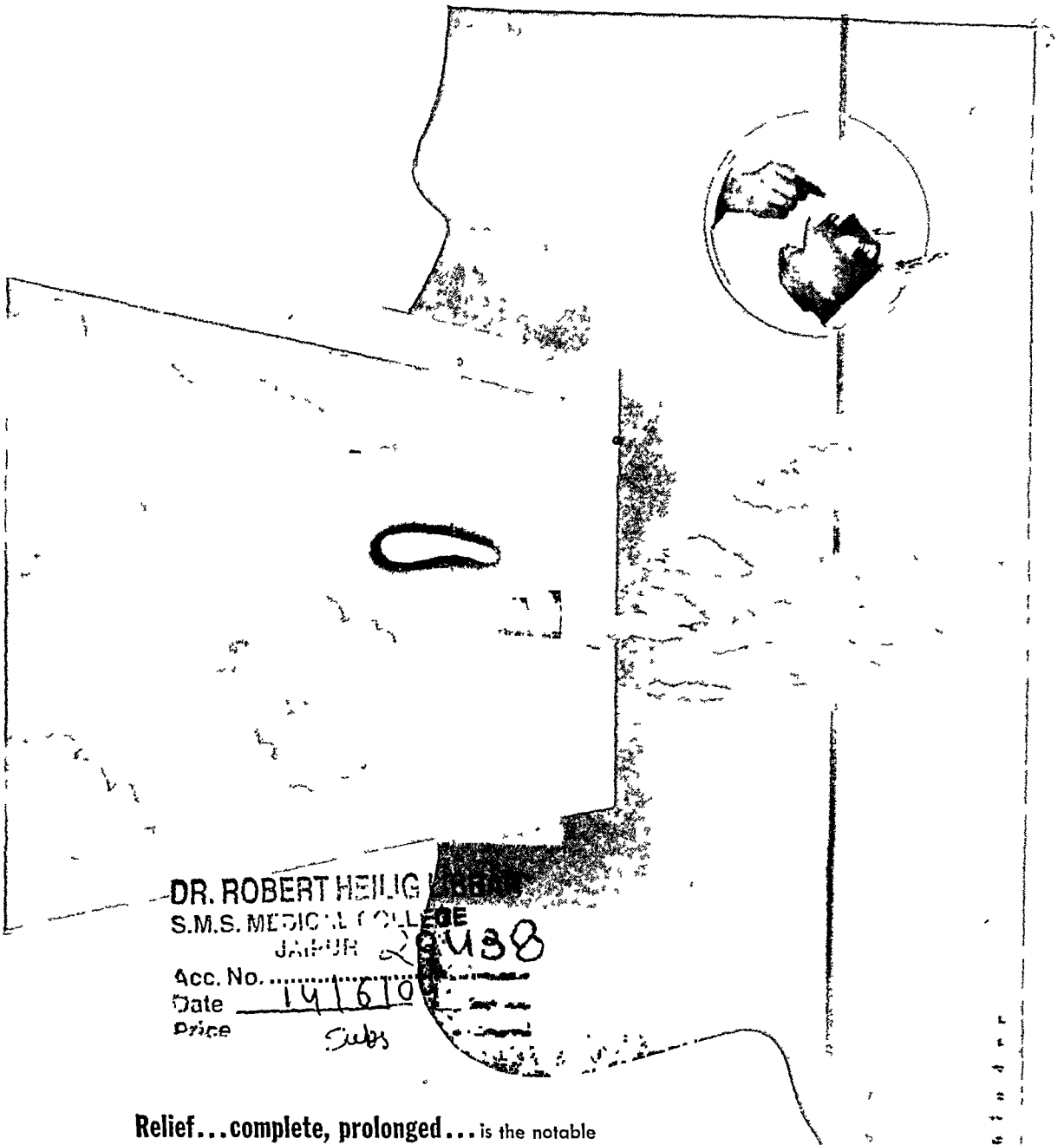
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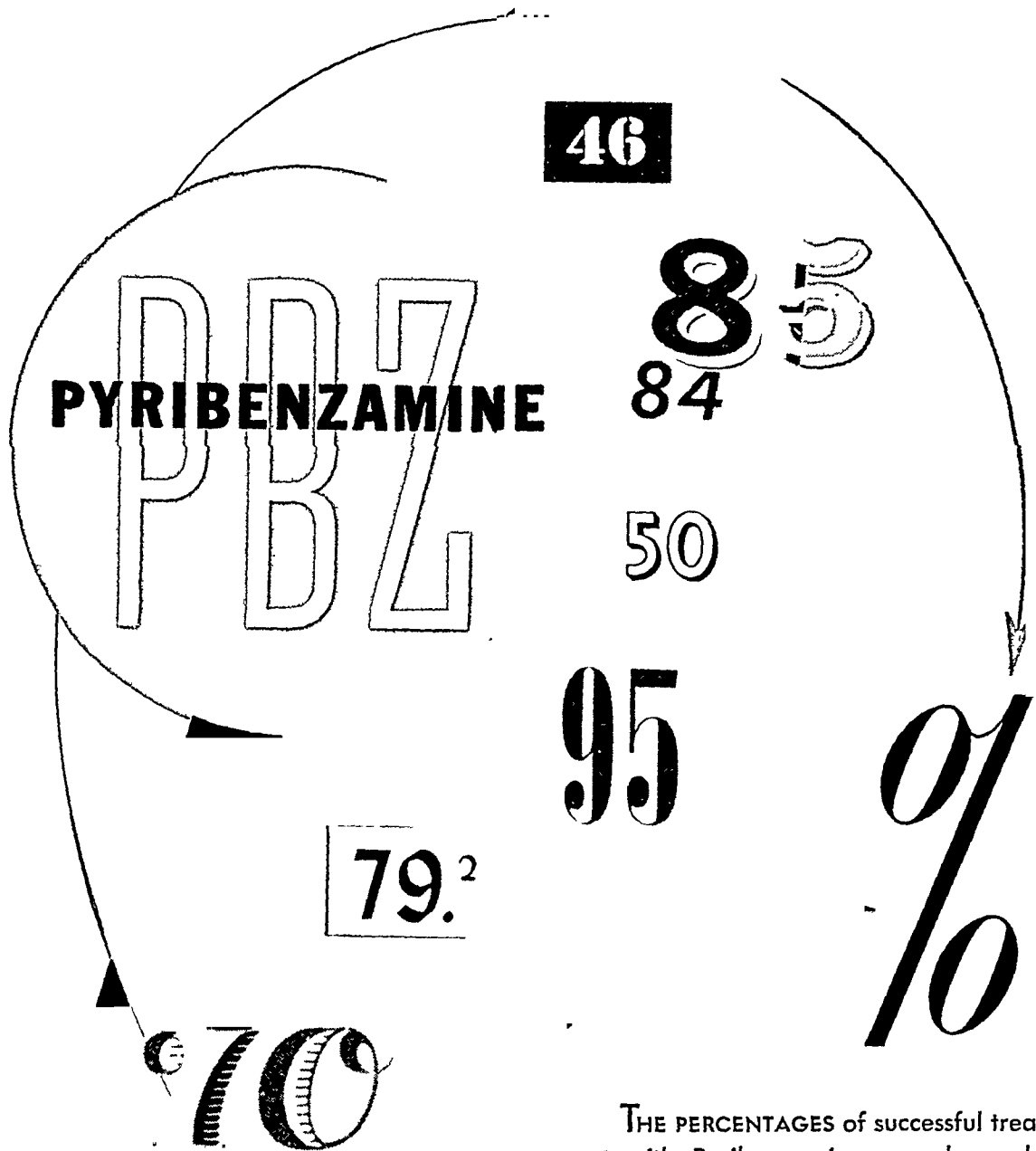
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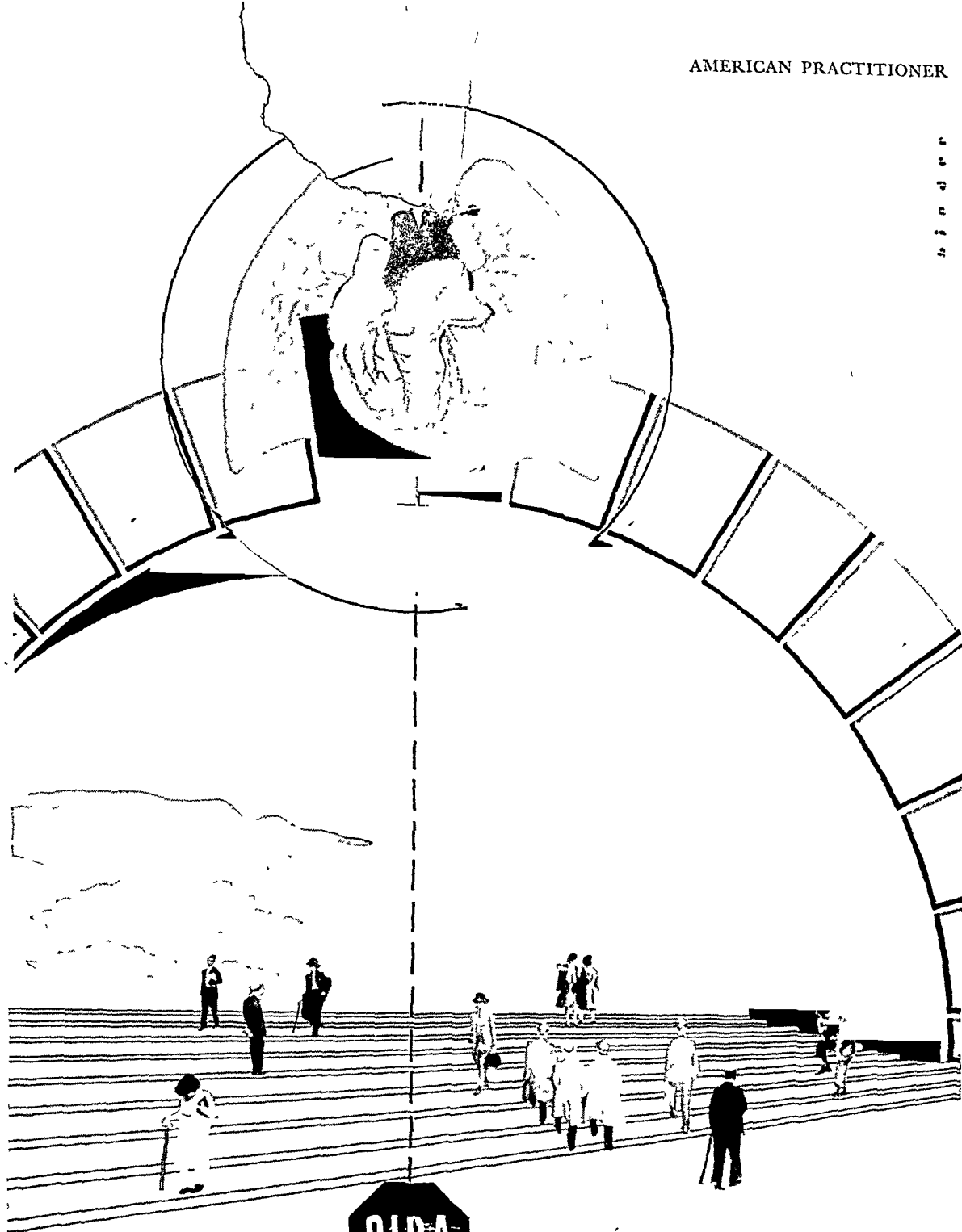
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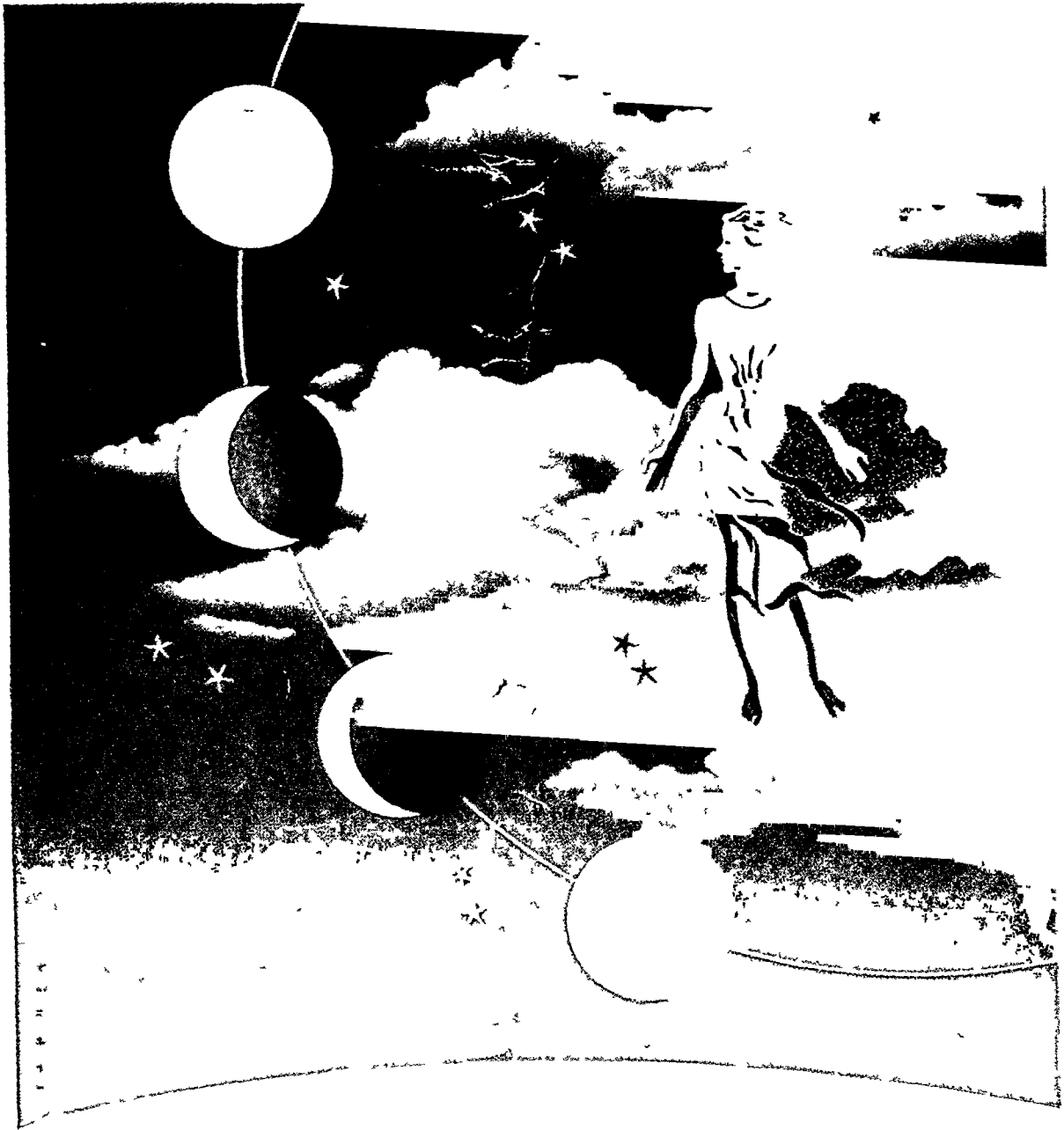
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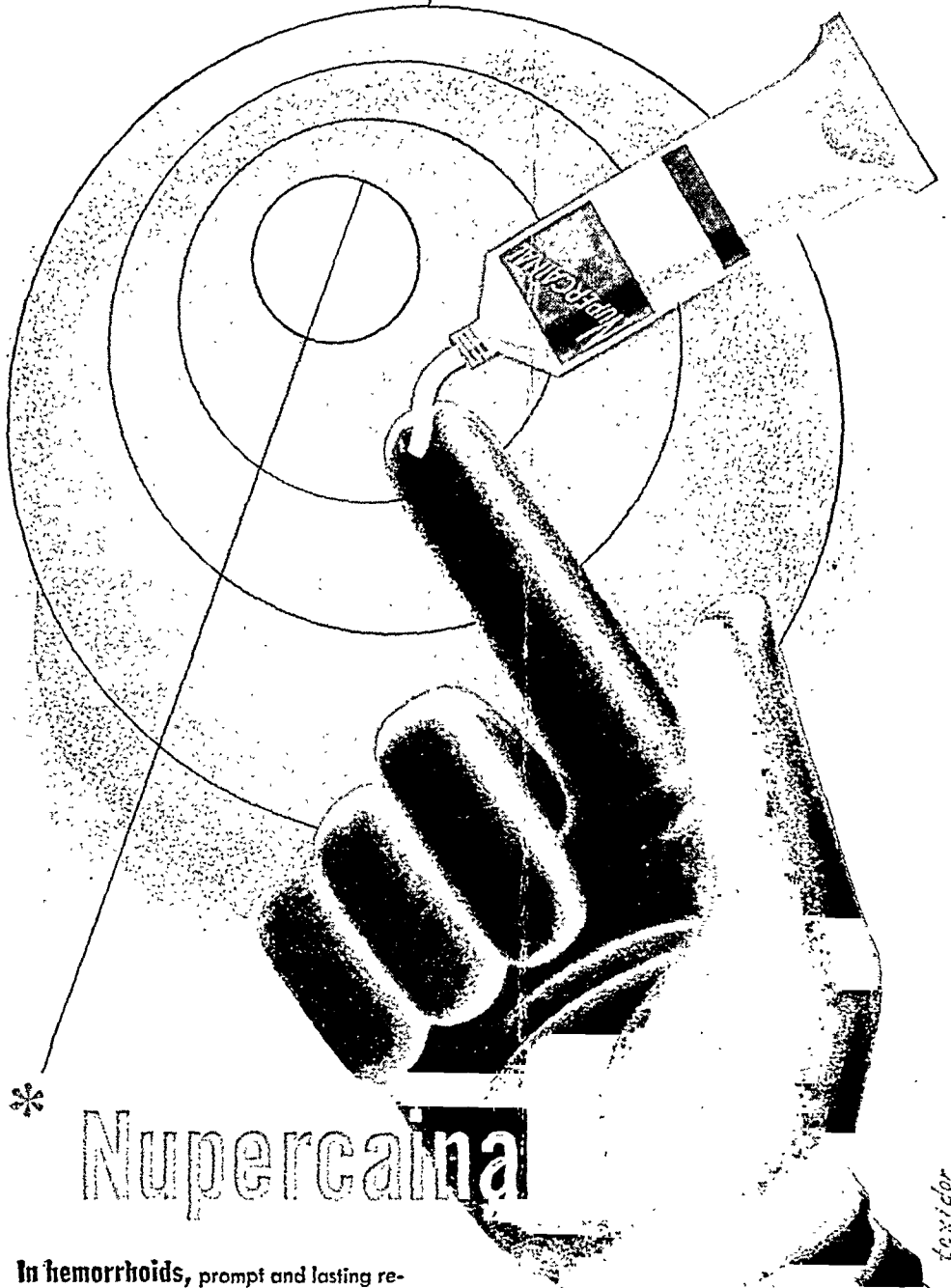
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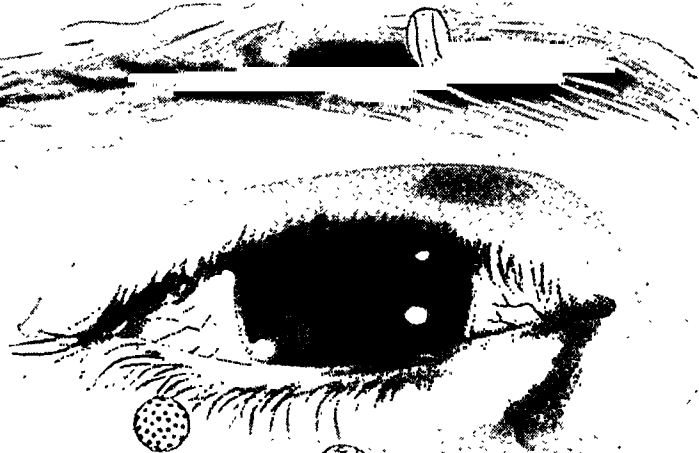


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*In this and in following issues from time to time, AMERICAN PRACTITIONER will present papers from a symposium on medicolegal problems presented under the co-sponsorship of the Institute of Medicine of Chicago and the Chicago Bar Association.*

*These papers deal with subjects which are of great importance to all practicing physicians and particularly to those doing general medicine. They concern matters on which we are often called to give opinions and about which many of us unfortunately are but poorly informed. In these papers the experts give us answers to many of these questions and the discussion which follows the paper brings out questions which may arise in the mind of the reader. Other papers in the series will deal with operations to produce sterility, trauma and tumors in industrial medicine, postmortem examinations, and expert testimony.*

## Artificial Insemination: Its Medicolegal Implications A Symposium

### Medical Aspects

J. P. GREENHILL,<sup>†</sup> M.D.

By artificial insemination I mean the introduction of semen into the genital tract of the female without sexual intercourse. There are two types of artificial insemination, one in which the husband's semen is used, and the other one in which semen obtained from a donor is employed. The use of a husband's semen is a medical problem and one need not be concerned about legal entanglements. On the other hand, many questions arise when semen from a person other than the husband is used. There are not only legal but religious aspects as well.

It is most unfortunate that during the last few years the lay press of our country has seen fit to sensationalize artificial insemination or as it is popularly known, "test-tube" babies. These news items have given the laity two impressions. The first is that the procedure is fairly new and the second that almost any mature woman can readily have a baby without any risks if a doctor will inject semen into her. Both impressions are erroneous. Artificial insemination has been practiced for a long time both in animals and in man and there are dangers connected with the procedure.

The first scientific research in artificial insemination of domestic animals was conducted as long ago as 1780 by an Italian physiologist, the Abbate Spallanzani on a dog. From these experiments the science of artificial insemination in animals spread to huge proportions. In modern times the leader in this field

was a Russian investigator Ivanoff who was the first to undertake successfully the artificial insemination of cattle and sheep. By 1938 the number of animals inseminated in Russia was as follows: 120,000 mares, 1,200,000 cows and 15,000,000 sheep. The Russian Ministry of Agriculture sponsored Ivanoff's work. In the United States the first co-operative artificial cattle breeding association was organized in 1938 and by October 1944 there were 100 such co-operative organizations with an enrollment of 230,000 cows.

Artificial insemination in animals possesses a number of advantages over natural breeding. The chief advantage is that it increases the usefulness of superior sires to an extraordinary degree. For example, the semen from one bull may be used to inseminate 500 cows. The percentage of success is extremely high. In sheep, for example, Quinlan and his associates obtained 95 per cent pregnancies using fresh semen at three successive heat periods. Special methods have been devised not only for obtaining semen and keeping it sterile, but also for shipping the semen to various parts of the country. By proper packing and refrigeration semen in transit up to 80 hours can be used successfully.

A second advantage of artificial insemination in animals is the full utilization of sires that have proved themselves able to transmit desirable characteristics. Artificial insemination has been used not only in cattle and sheep but also in horses, swine, birds and fowl.

In human beings, also, artificial insemination is not

<sup>†</sup> Professor of Gynecology, Cook County Post-Graduate School; Attending Gynecologist, Michael Reese Hospital, Chicago.



new. The first one to employ it was John Hunter who was born in 1728 and died in 1793. The exact year in which Hunter carried out artificial insemination in a case of hypospadias is unknown. Hunter's case was reported by Hume in 1799 and it is possible that Hunter's insemination in the human being was *done even before Spallanzani's experiment in the dog*. The first successful case of artificial insemination in the United States was reported by J. Marion Sims in 1866. In this case Sims used the husband's semen and success resulted after many injections. In six other cases the results were unfavorable. Sims later considered artificial insemination to be immoral medical practice.

In a series of 2,000 sterile couples Schultze resorted to artificial insemination in 102 cases with successes in only 15 (15 per cent). Schorohowa reported 22 successful cases among 55 (40 per cent) but his statistics are open to question. Cary reported a series of 17 cases in which the husband was infertile and the wife was inseminated with donor semen from one to six times with eight successes (47 per cent), and 18 cases in which the husband's specimen was instilled into the uterus with four pregnancies (22 per cent) resulting. Guttmacher was able to obtain 17 pregnancies in a series of 27 cases using semen from unrelated fertile donors (63 per cent). Hence, the results in human beings while good are far from perfect and much inferior to those in animals.

In 1941 Seymour and Koerner reported data concerning nearly 10,000 pregnancies that had been obtained through artificial insemination in the United States. However, two-thirds of these pregnancies were effected through utilization of the husband's semen alone and only one-third through the use of donor's semen. I performed my first successful artificial insemination in 1923.

#### INDICATIONS

In human beings there are really only two indications for artificially inseminating a husband's spermatozoa: (1) Inability of the husband to deposit the semen in the vagina and (2) inability of the spermatozoa to gain access to the uterine cavity from the vagina. The reason for a husband's inability to deposit his semen in the vagina may be pronounced hypospadias. That is a condition of the male organ in which the opening is not at the extreme end but on the under surface. As a result of this misplaced opening the semen cannot be ejaculated into the vagina at the time of sexual intercourse. Another reason for a husband's inability to deposit the semen in his wife's vagina is premature ejaculation before insertion of the penis into the vagina. Naturally in such instances

the semen is wasted. Another important reason but fortunately a rare one, is definite dyspareunia; that is, severe pain experienced by the wife during attempts at intercourse. The cause may be physical or psychic. The latter is difficult to overcome.

In nearly all cases in which coitus can take place normally but the spermatozoa do not reach the uterine cavity, the fault lies in a grossly abnormal discharge from the neck of the womb which prevents the spermatozoa from gaining access to the womb.

The indications for artificial insemination with a donor's semen are (1) complete absence of sperm, (2) grossly defective sperm (either decidedly diminished number, defective motility or excessive incidence of deformed sperm), (3) the likelihood of inheriting a disease (rare) and (4) if a woman has given birth to a baby with erythroblastosis foetalis. This disease of the newborn occurs in the children of a small percentage of couples (2 per cent) in whom there is an incompatibility of the blood as regards the Rh factor. When a woman has given birth to one or more erythroblastotic babies, the chances for obtaining a healthy baby procreated by the same father are at present remote. In these cases the use of semen from a donor who has the same Rh (which is nearly always Rh negative) as the mother is definitely worthwhile for couples who are anxious to have a child.

#### USING THE HUSBAND'S SEMEN

When the husband's semen is to be used the physician must first ascertain that the sperm are normal in number, form, motility and endurance and that no infection is present. The wife must have no abnormalities of the internal genital organs. Of course, the physician must also prove that the tubes are patent and eggs are present. Furthermore, he should warn both the husband and the wife that probably many attempts will have to be made over a period of a few months. It does not often happen that fertilization follows a single insemination any more than impregnation occurs after a single natural act of coitus.

The most favorable time for artificial insemination is at the time of ovulation. This is the time when an egg is ripe to be fertilized. There is only one egg each month in normally menstruating women and its life is short. Therefore, it is important to know the exact time during which to perform the artificial insemination.

Unfortunately at the present time, we do not possess any method of determining with certainty the time of ovulation in women. Nevertheless, we have means of determining ovulation in some women, especially if a combination of procedures is used.

Despite the fact that one cannot determine exactly

when a woman ovulates each month it is known that in the majority of women who menstruate fairly regularly ovulation takes place between the 12th and the 16th day after the beginning of a menstrual cycle. Since the life of spermatozoa is probably not more than 48 or 72 hours and the life of an ovum less than 24 hours (probably only 12 hours), insemination must take place within two or three days of ovulation. Therefore artificial insemination should be practiced between the 10th and the 17th day of a cycle. During these eight days semen should be obtained three or preferably four times. The specimens of semen should be collected in a clean wide-mouthed jar (2 oz. size), and not in a condom.

Of course, not all women menstruate approximately every 28 days. We can readily determine the best days for insemination regardless of the length of the menstrual cycle because we know that in most cases the egg ripens and therefore is ready to be fertilized about 14 days before the next menstrual period would begin. Roughly for women with a 30-day cycle we inseminate from the 12th to the 19th day, for a 35-day cycle from the 17th to the 24th day, et cetera.

The ideal arrangement for collecting the husband's semen for purposes of insemination is to have the couple obtain the specimen in a room in the physician's suite. This is perhaps the only way a husband can feel certain that his wife will not substitute semen from someone else if she foolishly or otherwise suspects that there is something wrong with him. An alternative to this plan is for the couple to go to a hotel near the doctor's office and bring the specimen to the physician immediately after coitus. The least satisfactory procedure is for the couple to obtain the specimen at home and bring it to the physician's office. To allay any possible suspicions on the part of either the husband or the wife that the one who brings the specimen will substitute semen from someone else, both the husband and the wife should present themselves at the physician's office with each specimen. While these precautions may seem severe they are the best guarantee against possible lawsuits involving the physician.

In my opinion it is useless to inseminate defective sperm (as to number, motility or excessive abnormalities) in cases in which normal coitus can take place. In such cases the husband's semen alone should not be used, and either a donor's semen or a combination of the husband's and a donor's semen should be tried. In a few of my successful cases of insemination I combined the husband's semen (defective in number and motility) with a donor's semen; in these cases the parents can at least hope that the offspring was really the husband's.

In cases of faulty deposition in the vagina it is only necessary to place the semen in the vagina at the neck of the womb. However, when the latter is the responsible factor, as can be determined by various tests, it is essential to place the semen in the uterine cavity beyond the neck of the womb. This procedure must be carried out with the utmost aseptic care and only after the physician has convinced himself that no infection exists in the woman's pelvis. The reason for this meticulous care is that when semen is injected into the uterine cavity, infection of the pelvic organs may sometimes follow.

For insemination into the uterus a special syringe is necessary but for insemination into the vagina any syringe or even a glass pipet will suffice.

#### USING A DONOR'S SEMEN

Great care must be exercised in selecting candidates for artificial insemination when donor's semen is to be used. Because of the recent propaganda in newspapers and magazines, a large number of infertile couples have been asking physicians for "test-tube" babies. Some couples come with an almost hysterical exaltation expecting a baby after a single visit to the doctor and they are greatly disappointed when told the truth about artificial insemination. Before undertaking artificial insemination in which a donor's semen is involved, the physician must consider the ethical, legal and religious aspects of this procedure.

The number of couples accepted for artificial insemination must be limited and the choice based on morals, health and education. While it is true that among the most grateful people in the world are couples given a baby through artificial insemination, there should not be any semblance of "mass production" in this matter.

The physician should have a heart-to-heart talk with both the husband and the wife and he should assure himself that he is morally justified in carrying out artificial insemination in any such couple. From the physical standpoint, the physician must be sure that the husband has no sperm and that the wife has no abnormalities of the genital organs, that her tubes are patent and that she has ova. Furthermore, both the husband and the wife must be in excellent physical and mental condition and their Wassermann reactions must be negative.

Of great importance is the selection of a proper donor. An individual must be chosen who bears certain resemblances to the sterile husband not only racially and physically but also emotionally and temperamentally. For example, it might be embarrassing in later life if a tall blond, placid type of donor

were selected for a short, swarthy, highly emotional couple. The donor must have no inheritable taint such as epilepsy or diabetes, he must have a negative Wassermann or Kahn test and preferably, though not necessarily he should be married and have normal children. Of course his sperm must be normal. A good source of donors is interns in hospitals, most of whom are happy to earn extra money. The price paid for each specimen varies from \$5.00 to \$10.00. If no pregnancy occurs after a trial of six months with one donor, it is advisable to secure another donor. Recently I began testing all donors and the women who are to be inseminated for the Rh factor.

The physician must arrange for the collection of the donor's semen and the insemination in such a way that the donor cannot possibly find out who is to receive his spermatozoa. Likewise the recipient should not be able to discover who the donor is. There are many valid reasons for this, chiefly the possibility of blackmail on the part of the donor and the risk of the transference of affection from the recipient to the donor. To eliminate all risk the donor should be asked to bring his specimen to a different place from that where the insemination is to be performed. If the specimen is to be delivered to the physician's office it should be brought to a side door during the physician's regular office hours when there are many patients so that the donor could not possibly identify the recipient even if he watched every woman who left the office. Of course, the physician should use his judgment in selecting a donor who would not be so low morally as to resort to dishonesty.

#### TECHNIC OF INSEMINATION

The patient is placed on the examining table, a speculum is inserted and the vagina and neck of the womb are cleansed with cotton. If there is a tenacious or purulent discharge in the neck of the uterus it is easily removed by aspirating with a syringe without a needle. The semen is drawn up into the sterile syringe and deposited at the neck of the womb. If the trouble lies inside the neck of the uterus the tip of a cannula, attached to the syringe, is carefully and slowly inserted into the cervical canal past the internal os for at least 1 cm. An antiseptic should not be used in the cervical canal because it may kill the sperm. Nor should a tenaculum be used on the cervix. Then about two or three drops of semen are gently and slowly injected into the uterine cavity. If more than this small amount is used or if the manipulations are too rough, the semen will be expelled from the uterus. After the few drops of semen are inserted into the uterus, the cannula is withdrawn gently. A portion of the rest of the semen is gently

injected into the cervical canal and the balance is placed in the vaginal vault. The speculum is carefully removed and the patient's legs are stretched out on the examining table where she remains for half an hour. In many cases the speculum is left in the vagina in such a way that the seminal pool bathes the external opening of the womb. If there is any dripping from the vagina after the patient gets up, the patient should wear a vulvar pad. There is no need to restrict her activities after insemination.

#### THE LEGAL ASPECT

Beardsley pointed out that the Supreme Court of Ontario in 1921 sustained a charge of adultery in a case in which donor semen was used in artificial insemination. Folsome emphasizes that in addition to the charges of "adultery in the test tube" the child may be declared illegitimate and many legalities may surround any of the parties involved in the procedure. The donor may be named the correspondent in a divorce case by the husband and the donor may become a contender in inheritance litigation should he learn the identity of the child. Adoption proceedings while assuring some degree of safety to the child provoke undesirable publicity which may frustrate the very purpose for which artificial insemination was initiated; that is, to produce a child from a childless couple. Folsome maintains that until public opinion is molded and safe and sane legal rules coupled with court opinions have removed the legalistic impediments from artificial insemination using donor's semen, it seems obvious that any system of affidavits based on embarrassing confidences are worthless as protection for any of the parties concerned. However, Cary believes that a simple written consent signed by the husband and the wife and histories filed indicating that both parties have submitted to preparatory examinations should constitute adequate protection. Seymour and Koerner insist on having the husband and the wife sign an elaborate document.

A very significant editorial appeared in *The Journal of the American Medical Association*. It is as follows:

Whether a child begotten from artificial insemination is legitimate or illegitimate according to the law is an important question. If the child is illegitimate and if the husband of its mother fails to adopt it legally, the child does not acquire inheritable rights from the husband. A child is legitimate if its parents are intermarried when it is begotten or born. Statutes generally legitimize also the issue of illicit intercourse if the parents intermarry, even though the intermarriage occurs after birth. The fact that conception is effected not by adultery or fornication but by a method not involving sexual intercourse does not in principle seem to alter the concept of legitimacy. This concept

seems to demand that the child be the actual offspring of the husband of the mother of the child.

The presumption of law that a child born during wedlock is legitimate is not absolute and conclusive under all circumstances. Even at early common law the presumption was overcome by proof of the husband's sterility. Today the presumption as to legitimacy is more easily controverted than it was in earlier times. Now it is generally recognized by the courts that a child is illegitimate, though born or begotten during marriage, when it is impossible that its mother's husband could have been its father. Every species of legal evidence tending to this conclusion is admissible on the trial of the issue as to its legitimacy.

Artificial insemination can be effected from only two sources: from the semen of the husband of the prospective mother and from the semen of some other male. If the semen of the husband is used, the child obviously is as legitimate as if it were the result of normal and usual intercourse between husband and wife. If the semen of some other male is utilized the resulting child would seem to be illegitimate. The fact that the husband has freely consented to the artificial insemination does not have a bearing on the question of the child's legitimacy. If it did, by similar reasoning it might be urged that the fact that a husband had consented to the commission of adultery by his wife would legitimize the issue resulting from the adulterous connection.

Some advise that all question as to the legitimacy of a child produced from the semen of a male other than the husband of the mother be ignored, apparently relying on the secrecy attendant on artificial insemination and on the presumption of law that a child born during wedlock is legitimate. Such reliance, however, disregards the apparent intent of the husband to confer on the child the rights incident to legitimacy. Those rights, if illegitimacy or even doubt as to legitimacy is frankly recognized, can be assured by adoption proceedings, which ordinarily are comparatively simple.

## Legal Aspects

JAMES F. WRIGHT,† Esq.

There may be some exceptional cases where artificial insemination is proper. I do not disagree with the doctors about that; there probably are some. In those exceptional cases, where the husband is used as the donor (and I think ordinarily the husband is used very rarely as the donor) there can be very little dispute insofar as the legal aspects are concerned. The husband, of course, has consented and so has the wife, and the resulting child is the offspring of the husband and the wife.

The ordinary rules of law governing doctors in situations of that kind are applicable and we get those rules from the cases that have been decided principally in malpractice suits. There the rules have been laid down that a doctor must use ordinary and rea-

In many instances of artificial insemination, perhaps in a great majority, the facts may never be known to any one other than husband and wife and the physician involved. There is the possibility, however, that interested relatives may learn of the circumstances and may procure the evidence necessary to overcome the presumption of legitimacy and may thus deprive the child of a share of intestate property. It is the just due of the child that false pride or considerations of delicacy be put aside and that it be given, through adoption proceedings, the protection intended by the husband of the mother when he consents to the artificial insemination of his wife.

## CONCLUSION

The first thing to be done in the matter of artificial insemination in which a donor's semen is used is to clarify the legal aspect. When the husband's semen is used there is, of course, no legal question. Should the courts decide, however, with some degree of unanimity, that artificial insemination of a woman with a donor's semen constitutes adultery then we physicians will have to discontinue performing this procedure. Even though there is great secrecy about the matter and the couple is elated with their baby, one never knows when a husband may change his attitude toward the offspring. At the present time we are gambling because there are no legal rulings, except one, against the procedure.

Should the courts decide that artificial insemination is a purely medical and social problem and involves no legal entanglements, then we may safely continue our humanitarian efforts.

sonable care and skill in the practice of his profession, and that he must exercise his best judgment. Those rules of law apply to the conduct of the physician or surgeon treating his patients regardless of what kinds of cases he may be presented with. Thus in a case of the character under discussion he would have to use ordinary care in examining his patient and in examining the donor, and in actually carrying out the technic of the artificial insemination. And that would all be a matter for his judgment in view of his learning and his study of the case.

When, however, you go out of the field of using the husband, and use a third-party donor, then the doctor, to protect himself, must naturally obtain the consent of his patient, the prospective mother, and he should also obtain the consent of the husband. Sub-

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sequently something might develop to cause the husband to institute legal proceedings against the doctor, saying that this had been performed without his consent, and that he had been damaged or aggrieved by the technic. Those consents should be in writing and should be witnessed, for the doctor's own protection. I think, also, when a doctor uses some third party as the donor, he should obtain the consent of the donor himself, so that that donor will be estopped to say that some fraudulent practice has been perpetrated upon him and that he has been used in an experiment.

There is another complication that might possibly arise, although I know of no case upon the subject. That is where the donor is married, and his wife might feel aggrieved. It might be well for the doctor to call her in and obtain her consent, also.

I feel that when we get really down to bedrock and discuss this situation, the legal principles concerning the physician are not complicated. As I have said before, he must use ordinary care, and that is basic, that is fundamental. There is, however, a bigger problem, the social problem; and that is the problem that I think we here tonight should consider more than the responsibility of the doctor in using care or skill in performing his operation.

You may consider, of course, that many and various problems arise insofar as the husband of this mother is concerned, where a third-party donor is used. For example, the prospective mother goes to the doctor, this procedure is carried out, and a child is born. Who is the father of that child? Certainly not the husband, but some third party. Maybe they know who he is and maybe they do not.

If you are going to consider that fact, think also of the matter of the name. What would be the name of this offspring? Would he have the husband's name? I suppose he would. He might assume it, but really, it wouldn't be his name, unless we say our name is anything we happen to call ourselves. Then you have the other traits, such as complexion, color of hair and racial traits that might creep in.

Something was said here tonight about adoption. Statements have been made in various medical journals from time to time, that where a procedure of this kind is to be carried out, the husband of the mother should, as soon as possible, adopt the child. How are you going to meet that situation? Are you going to procure from him before any such procedure is undertaken some agreement, or some contract by which he says that he will agree to adopt the offspring? If you are, how can you enforce it? Frankly, I know of no method by which you can compel a man to adopt a child. I do not know how you could enforce that contract.

Assume that you could, then what would that bring? It would, in all likelihood, cause a disagreement between the couple, a discord, and possibly a separation. In a matter of this kind, society in general and the state, too, has an interest.

The doctors speak about this question as one of pure science, but I don't believe that lawyers can speak about it in that way at all, because law is founded upon good morals and what is best for society in general. That is what makes the law.

We must, of course, look to the status of this offspring. I realize that this is a mixed gathering here tonight, but the courts of Illinois, and practically every other state, have had under consideration not children born from artificial insemination, but children born where the husband of the woman producing the child is not its father. Under the decisions of this state, a married woman's child begotten by one who is not the husband of its mother is, in the language of the courts, a bastard. The true test in determining—I am quoting from the Illinois courts—whether a child born in lawful wedlock is legitimate, is whether the husband of the woman who gives birth to the child is its father.

Going back to this procedure, what would the status of the child be? While, of course, the legal presumption obtains that every child born in wedlock is legitimate, it is a presumption which is rebuttable. A legitimate child is one born in lawful wedlock and an illegitimate child is one begotten and born out of wedlock, yet it does not follow that every child born in wedlock is legitimate. A test applied by some courts, and stated by them to be the correct test, is whether the husband of the woman who gives birth to the child is its father.

Consider, if you will for a moment, that the courts of this state and many others have held that the law does not impose upon the husband any duty to support or contribute to the support of his wife's bastard child. Now you may easily see why this practice of artificial insemination may from the standpoint of the state be considered dangerous. Who will support this child, if not the husband of this mother who produced the child? Will it be thrown back on to the state, or on to society in general, or will it be up to the mother to furnish support?

You may also consider the situation that might occur where both the husband and wife agree to have the wife artificially inseminated by sperm from someone other than the husband, both having agreed because they thought it impossible for the husband to become a natural father. It has been stated here that tests can be made. Maybe they are accurate; and maybe some of the tests are not so accurate. Just

suppose that here is a woman who does have a child by this method, thinking that the husband could not be a natural father, and that after that child is born, they have a natural child of their own. How about that first child? How is he to be treated? Is he to be pushed aside because the father is aware of the fact that the last child is his and the first one belongs to someone else, whom he doesn't know? That may lead to a disruption of the marriage. That may lead to a separation. No one can tell. But it raises a problem, and a problem that must be considered.

In a rather early case here the court said that where a child is born in wedlock, and someone other than the husband of its mother is the father, then the mother has been guilty of adultery. That case was decided in 1891, and I suppose the judges who wrote the opinion did not have in mind the great strides that might be made within the next 50 years in the medical profession, and they didn't know that this thing might be possible. Nevertheless, we have that fundamental definition handed down by our courts, and it has not been reversed, so far as I know.

Stress is sometimes laid upon the distinction between the act of adultery and the consequences of it. The contention has been made that insemination or pregnancy is merely the result of adultery. One court said that, and that as a matter of law, adultery is confined to the act of sexual intercourse in the ordinary accepted term.

Is it necessary to draw distinctions between an act of incontinence of a wife and similar act by a husband, or as to whether or not sexual intercourse between unmarried persons constitutes adultery? Wherever the term adultery is defined, we almost always find the words sexual intercourse, or some synonymous expression used to describe one of the principal ingredients or characteristics of the offense. It is said in the American and English Encyclopedia of Law, second edition, Volume I, page 747, that adultery by the common law is criminal conversation with another man's wife. According to the canon or ecclesiastical law, adultery was sexual connection between a man and a woman of whom one, at least, was lawfully married to a third person. The ecclesiastical law regarded adultery as a sin arising out of the marriage relation. In Blackstone, page 139, is found the definition: "adultery, or criminal conversation with a man's wife." Other definitions that have been employed are: "a violation of the marriage bed;" "the voluntary sexual intercourse of a married person with one of the opposite sex;" "the sin of incontinence." Some text writers have stated that there must be actual sexual intercourse, and that no proof of indecent liberties would be sufficient.

One article written on the subject of artificial insemination cited a Kansas case in an endeavor to show that by this means of having children the mother was not guilty of adultery. That Kansas case, however, was a case where the charge was rape, and when the court spoke of sexual intercourse and defined it, the court was really talking about rape.

The marriage tie has as one of its primary objects the perpetuation of the human race. When our laws were written the subject of artificial insemination undoubtedly never entered the minds of the lawmakers, for if it had, statutes would have been enacted concerning one of the most sacred of the marital rights of husband and wife. It has been said that the essence of the offense of adultery consists not in the moral turpitude of the act of sexual intercourse, but in the voluntary surrender to another person of the reproductive powers or faculties of the given person. Any submission of those powers to the service or enjoyment of any person other than the husband or wife comes within what many writers have declared to be the true definition of adultery. The fact that it has been held by some courts that anything short of actual sexual intercourse, no matter how indecent or immoral the acts may be, does not constitute adultery, strengthens the view that it is not the moral turpitude that is involved, but the invasion of the reproductive function. There can be no adultery so long as nothing takes place which can by any possibility affect that function. Therefore, unless and until there is actual sexual intercourse, there can be no adultery.

To argue from that, however, that adultery necessarily begins and ends there, is utterly fallacious. It has been held that sexual intercourse is adulterous because in the case of the woman it involves the possibility of introducing into the family of the husband a false strain of blood, and that any act on the part of the wife which does that would therefore be adulterous. It appears that the idea that such a thing could be accomplished in any other manner than the natural manner, probably never entered the minds of those writing the statutes. If such an act as here described, that is, introducing artificially the sperm of some man other than a woman's husband, were done against her will, it is conceivable the act might constitute rape.

While I am fully aware that some of the articles written upon this subject have contended that it would not be adultery for a woman living with her husband to produce by artificial insemination a child of which some man other than her husband is the father, it seems to me that that is a most erroneous conclusion. If such a thing has not been declared by our courts to be adultery, I, for one, believe it should, on the grounds of public policy, if for no other reason.

If it is wrong to artificially stop a life by abortion when no real medical need exists, then why is it not likewise wrong to start a life artificially? Certainly the human life is not a toy to be started or stopped through some whim or caprice. There are those, and I think they are legion, who believe that there is something sacred about life, just as there is about the marital relationship. I realize that I was not asked to deliver a sermon, but what is the law founded upon except upon good morals?

There are other questions which come to mind in considering this subject. One is in regard to real estate titles, the statutes of descent and distribution. From whom could this child inherit? Would he inherit from the husband of his mother, when the husband had nothing to do with producing this offspring?

Take the converse of that. Assume that there had been no adoption and that the husband for many years supported his wife's child and spent money on him, and then in later years became a pauper himself, while the child grew wealthy. Could that child be compelled to support that man who had supported him all of those years, when that man who had supported him was not his father and therefore, in law a stranger to him?

You, of course, may feel as some of the accounts in the newspapers, the journals and the magazines indicate that this matter of artificial insemination is something progressive, something new. You may believe that I am not progressive in taking the stand that I do. There are many, many legal questions that have not been solved by our courts. The questions have not been presented to them; they have not had occasion to pass upon them, and until they do, there is very little law upon the subject directly. We may by reason and by logic raise and answer a few questions. But until the courts have had more opportunity to consider the several propositions that from time to time may arise, we are not in a very good po-

sition, as you will see, to give any legal opinion that will amount to very much upon this subject.

I must say that I did not realize the widespread interest in artificial insemination until just recently. The journals say that many, many cases are performed. A good many of them probably are never recorded, and so we have no way of knowing just exactly how prevalent this practice is. I have been surprised, however, since the notice of this meeting was posted, how many attorneys around the courthouse stopped me and discussed the subject with me.

In view of this interest it seems to me that we may need some special statutes regarding this matter. We may need some plan of operation, and don't ask me what that plan is; I don't know. But I do believe that it is important to give it consideration. If it is important enough for these doctors to come here, if it is important enough for these various journals to write upon the subject, then the practice must be rather prevalent, and if it is, we can see where it may lead in the courts. And if that is true, we certainly need some sort of legislation.

I believe that some one of the numerous committees of the legislature should be appointed to give the subject some study and to report its findings. We, of course, haven't the opportunity to call in various and sundry men that have the information necessary to formulate statutes or laws, but the legislature has the facilities.

Until the lawmakers have acted and until the courts have ruled, we may be guided by a law that is all too often not referred to, and that is the moral law. In considering our subject tonight, it seems to me that that would be the law to follow. A very good definition was recently given by a court, when it said: "The moral law is the eternal and indestructible sense of justice and of right written by God on the living tablets of the human heart and revealed in His Holy Word."

## Discussion

CHAIRMAN FISHBEIN: \* The discussion from the legal aspect has obviously opened up several controversial points of view on the subject. I am again reminded that it is often impossible for the legislative bodies to anticipate the progress of medical science, or indeed, the progress of science generally. Often evidence is lacking upon which any court or any legislative body could make a decision, and that evidence is only to be accumulated out of experience. When sufficient experience has been accumulated and comes to light, in most instances the court acts. For instance, before we had an atomic bomb, we never had the question raised

as to whether or not the explosion of an atomic bomb would injure the blood of a human being so as to destroy a human being 20 or 30 months after the bomb had exploded. Until we have collected evidence on the subject, no one will be able to offer any legal opinions as to the use of a bomb which will have remote effects. The same thing applies, of course, to the gradual accumulation of evidence regarding artificial insemination. We are dealing here not with anything at all theoretical; we are dealing with a process in biology in which there are already accumulated many thousands of cases in medical records, although there may be very few cases in legal records. Obviously any group of lawmakers following the suggestion of Mr. Wright, would have to assemble scientific evidence before it endeavored to

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pass legislative enactments affecting the process. If they did not, they would be passing legislative enactments upon an emotional, rather than a scientific basis, and in scientific questions, we try as far as possible to keep away wholly from the emotional aspects of the subject, although even in courts of law it is very frequently difficult to avoid being emotional.

We have here many physicians, and as I have said, many distinguished men of the legal profession, who are capable of discussing this subject, and I am going to take the liberty of calling upon one or two physicians, and one or two members of the legal profession first, and then, of course, the meeting will be open for general questions or for general discussion. I see before me here Dr. Danforth, and I wonder if Dr. Danforth would care to discuss the subject for us.

DR. WILLIAM C. DANFORTH: Mr. Chairman, I can't discuss this question with any basis of experience, because it is a procedure which I have not carried out. I have been very much impressed by the remarks of Mr. Wright, who brought out a great many things which we doctors, I think, have not known about, or thought about, or considered. Of course most of us know very little about law, anyway. About the only law that most of us have occasion to run into is that which we meet when the policeman stops us on the street. Fortunately, most of us manage to evade the courtroom in the matter of malpractice procedures, although not invariably.

I think the implications as to the infant which Mr. Wright brings out are too strongly put for us to wholly ignore. It seems to me that anyone who wants to attempt this procedure, any physician who wants to attempt it, must consider them very, very thoroughly.

There are very definite medical dangers which may enter into the picture; the question of infection, which has already been dealt with by Dr. Greenhill. I think the public enthusiasm which has been stirred up somewhat by the newspapers has been wholly unfortunate, as I think has been alluded to by one of our speakers. I cannot personally feel any great degree of enthusiasm for it. I would rather not do it. The reasons for not doing it have already been set forth. Technically, of course, it can be done with due care on the part of the physician, with a reasonable degree of safety. The legal aspects of it really impress me very deeply. I am sorry I cannot talk any more authoritatively or any more at length about it, because my experience, as I say, has been very small. I think definitely the moral point of view is one we must consider very seriously; and I agree with the suggestion of Mr. Wright that, inasmuch as the procedure is now being used fairly frequently, there ought to be some study by the legislative body concerning it so that we may have some basis of law upon which to go.

CHAIRMAN FISHBEIN: I will ask Mr. Irwin, representing the legal profession, if he would say a few words.

MR. ROYAL W. IRWIN: The matter of the legal implications resulting from artificial insemination is a matter which I am sure has not been considered by the legal profession. I was quite interested in the remark the chairman made about how far the scientific world is ahead of the legal. It is a fact that for many years artificial insemination has been used. The legal profession has been slow to consider it from the legal standpoint.

There is just one thought that occurs to me, which I think goes one step beyond Mr. Wright, and that goes back to our own profession. We have in our work personal in-

jury cases, damage cases. The Bar Association has interested itself very greatly in the handling of those cases. It has been my observation that pretty nearly everybody has lost sight of the person who is most vitally interested in damage cases, and that is the injured man. I think we have all neglected the interests of the injured man.

That follows up in this way in this discussion. I have often marveled at the large families that some couples have brought into the world purely selfishly. A husband and wife decide between themselves that they want a child, purely selfishly. They are not thinking of the interests of that child that they are bringing into this world; they are thinking only of the pleasure that they will have as father and mother in raising that child. Whether posterity will be benefited by the bringing into the world of this child is a matter of no concern to them. They have a child because they want it, because they feel that they—they, not the child—will be happier by having this child. Extending that one step further in the question of artificial insemination, it seems to me that possibly from a moral standpoint, we ought to consider the rights of this unborn child that they are so eagerly attempting to accomplish, so eagerly attempting to bring into this world against its own will. Whether they are financially able to take that child and raise it; whether they have the moral background that is necessary to give the child the right start—all of those questions are not considered. It seems to me that this matter of artificial insemination is but the outgrowth of selfishness on the part of persons. I understand that women do have an urge, a desire to become a mother, a desire to have children and raise them, to exercise their function of motherhood, and it is a grand thing, a beautiful thought, there is no question about it.

But taking it more from a moral standpoint than from a legal standpoint, whether it is for the best interests of posterity that children be brought into the world in that manner is a debatable question. There must come a time, and it isn't very far distant, when there must be some limitation to the size of families. The world will sometime, and not very far distant, become over populated.

CHAIRMAN FISHBEIN: The subject leads into many different ramifications, as is clearly apparent. I thought when we ran our editorial, we had to some extent protected the rights of the child through the suggestion that such a child, when born, immediately undergo legal adoption by the parents. However, our laws regulating adoption have never kept up with science. The laws of adoption of the individual states are far behind scientific knowledge regarding what would be safe from the point of view of adopting a child, and even when we endeavor to control this by the most careful advice to father and mother, using all the best knowledge that science has, we well may make errors. Instances have occurred in which prospective parents have adopted a spastic child, or something of that sort, and that raises many serious points, so that adoption in itself would not necessarily be a suitable cure for the rights of the child under these circumstances.

We have here Dr. Koerner, of New York, who has had experience with this procedure.

DR. ALFRED KOERNER (New York City): Thank you very much, Mr. Chairman. It is a very unexpected pleasure and privilege to address you. I came here principally because I was enamored of the fact that Dr. Greenhill, who is the leading authority in medical matters of this kind and



other kinds having to do with gynecology, was discussing this subject.

I think this subject should be re-examined a little bit, after all the knowledge we have had placed before us this evening. As a representative of the Bar of the State of New York, and also as a practicing physician, I want to tell you that after some twelve years of work with it, there are many things to be said about it.

Dr. Greenhill, quoting Dr. Beardsley, cited the case of *Orford v. Orford*, appearing in 49 Ontario Law Reports. In that case, if you look it over, you will see that one Hotchkinson was found as a matter of fact by the court to have had carnal relations in the ordinary manner with the defendant. After finding that that was sufficient cause to grant a divorce in the action, the court felt constrained to consider artificial insemination, which at that point was no longer material, so after all, we as lawyers know that everything that is said from there on is *dicta* and cannot be taken as a basis for anything that has been adjudicated in this continent.

The only adjudication of this continent of which I am aware is a very recent case occurring in your own city in which Judge Feinberg, of a Cook County court, had a case very similar to this *Orford v. Orford*, and he there allowed a divorce on the basis, again, of sexual relationships in the ordinary event. However, again as *dicta*, he considered the question of artificial insemination, as to whether it could be or ever was a cause for the judgment that adultery had been performed, or could support an action in divorce, and as *dicta*—and we admit that it is *dicta*—he ruled that it could not be. He said it could not be. There was no written opinion in that case. So there you have it, gentlemen. You have two cases of *dicta*, one on one side, one on the other. You may take your choice.

I was very much interested in what my colleague, Mr. Wright, had to say on this subject, but I was a little bit disturbed by the fact that no basis was laid for discussing the matter, insofar as to tell us as an audience the incidence of sterility in this country. We must remember that in this country one out of every ten married couples is involuntarily sterile. Gentlemen, that is a serious problem. That isn't a problem that we, the other nine—I hope we are the other nine—can easily wave aside. These people have a right to be considered. They are very numerous. They are much more numerous than the sufferers of poliomyelitis, about whom we make very considerable effort.

Those people are married; they have decided to take each other for better or for worse. They want a family, and I will agree absolutely with the last speaker, insofar as it is a very essential element to discover whether or not the prospective parents are capable of supporting the child in a proper manner, before essaying to bring him into the world. But that is true of any couple, whether by artificial insemination or any other way. And how many of us bother to find out about it? Do we say to the alcoholic, "We will put you in jail because you might beget a child and we can't ask that child whether he wants to come?" Unfortunately, although we ought to, we don't.

We who are doing this work like to look on artificial insemination in a much milder manner than most of the speakers tonight have given me to believe. We like to consider that at least one of the parties who comes to us is on the verge of despair, many on the verge of divorce; that those people are, at least to the extent of 50 per cent, de-

termined that they will have that child. Let us say the husband knows, or says, or commits himself in no way. The wife does. She comes there voluntarily, no one points a gun at her. She comes there herself and wants a child.

We like to tell the husband what would happen if he refused, and if his wife was good enough to suggest adoption, and he agreed, "This child would be a stranger to both of you, but in this way the child is semi-adopted, it is one of yours. As to the other it is adopted; you may so consider it."

The question of adoption, ladies and gentlemen, has never recreated a bloodstream. The laws have been very liberal, from away back in Roman days. This does not go back to the common law at all. This goes back to Roman days. The Romans had long decided, being a colonizing people, a conquering people, and rather a slovenly people in the late empire days, that someone else should do the work for them. There were some very clever people who became prisoners of theirs, as a matter of course, and it became convenient to adopt them, to get the benefit of their work. Those things were done 2,000 years ago. Then adoption was used simply as a method of bringing in, legitimatizing someone else's offspring, as if it had been your offspring.

Someone might ask, since you can marry two people who have had an illegitimate child, and legitimize the child, why wouldn't it be a good idea to perform a second marriage ceremony in the case of all those who have had an artificially inseminated child? What would be the harm of having the second ceremony? At least you certainly would have a way of having the child made legitimate, and to him no one could raise a finger. After all, if you dig into the common law you will discover that the reason that we have such a thing as illicit intercourse entering into the question of adultery is a question, principally, of property rights. Our old ancestors were very proud of their possessions, and their possessions even went so far as having a wife, and they didn't want anybody to violate her, not because they loved her, because in many instances they certainly did not, but because she belonged to them. The old lock-and-key days are still known to all of us. That is only a question of property.

Mr. Wright, I think, said, in quoting a decision that I happen to have read, that one of the courts characterized bastardy as a voluntary surrender of the reproductive function. I don't really know what that is. I have studied that phrase for years now. I don't know what a voluntary surrender of the reproductive function may be. I imagine that every time a woman or man has intercourse, with the rarest exception of a gun pointing at them, it is voluntary. If it happens that fertilization should occur, and a conception takes place, and a child is born, that person has nothing more to do with it after that initial intercourse. He may interrupt it, true. He may cause an abortion. But he has nothing to do with it. It is voluntary and it is involuntary, if you know what I mean. But I don't really know what surrender there is of a voluntary relationship in artificial insemination, when the semen is introduced in a manner described.

Another point was brought out that there was something immoral about perpetuating a possible existence artificially. I imagine that "artificially" might, just for brevity, be characterized and defined as introducing something from without, extraneous to the organism. A person who is about to

die from a hemorrhage on the field of battle, from loss of blood, gets blood from a blood-bank artificially, yet he lives. Is there anything immoral about that? Is there anything immoral about introducing external situations which may either continue life in those who wish to live, or perfect it, or initiate it, in those who have a right to make a decision as to whether it should be initiated?

This question of a medicolegal meaning between the medical profession and the legal profession, in regard to artificial insemination, is not new, gentlemen. I just want to say one word in regard to a recent survey of the field, appearing in the *Medicolegal Criminological Review of England*, the issue of July-September 1944, in which the Bar of Great Britain, together with the medical profession, considered it. Judge Earengy, who happened to be present at the time, spoke of a case that has been quoted in *Time Magazine* most recently in this country, of *Russell v. Russell*. In this case Lord Dunedin said that fecundation *ab extra* is adultery, but the court assumed there was no child possible without sexual intercourse. As one of the speakers indicated, no concept was had by anyone that it was possible without intercourse, so really that was not relevant, although the gentlemen wrangled back and forth on the question of artificial insemination.

CHAIRMAN FISHBEIN: I know we all appreciate the very fine contribution of Dr. Koerner. I was familiar with the discussions that have taken place in Great Britain, and following the symposium to which he refers, the *British Medical Journal* and the *London Lancet* each printed dozens, if not scores of letters on the subject, arguing pro and con the aspects of the subject, and unfortunately the discussions invariably wandered to the moral side of the question. I believe we are concerned primarily as a scientific medical group meeting with the legal group, with the scientific and legal aspects. It may be impossible to separate the scientific and legal aspects, as Mr. Wright indicated.

I should like to say again that all of us represent again the proof of the fact that legislative enactment fails to recognize the existence of this procedure until difficulties arise under the law which cause it to go into the courts, and eventually there are decisions, and eventually legislation does catch up with medical processes that have been carried on for some time.

Dr. Koerner referred to blood transfusion. We do not have adequate legislation at all on our books covering the various problems that arise in relation to blood transfusion. I have no doubt that eventually the law will catch up with this procedure, inasmuch as five million Americans last year contributed blood which will be transfused into other people by a process somewhat similar to that used in artificial insemination.

MEMBER: I don't suppose we could expect very complete agreement on so controversial a subject. When this was mentioned to the committee of the Bar Association, of which I happen to be a member, I recall it was considered "too hot a potato" to handle at all in open discussion. I am glad to say the majority of the committee decided to the contrary.

It seems to me Mr. Wright discusses the legal question from the standpoint of what the law is, rather than from the standpoint of what the law should be. After all, adopted children were not permitted to inherit until legislation permitted them to do so. We could not eliminate

child labor until there was remedial legislation. It isn't a question of from whom a child born in this manner does inherit; it is a question of from whom he should inherit. Should he inherit from the husband of the mother, the husband who has voluntarily and willingly submitted to this operation, or technic, or whatever you may call it? That, it seems to me, is the basic problem, and the question of what the law is today is but an incident. We have to have law to control the atomic bomb. Maybe on a minor scale, as Dr. Fishbein has suggested, this is almost as startling as the atomic bomb, and needs legislation accordingly.

It seems to me—I can't very well speak from the standpoint of a mother—but it seems to me a woman might very well prefer to have a child who was her own, rather than a child she adopts. It seems to me a husband might very well prefer to have his wife have a child who is her own, rather than an adopted child. It seems to me a husband might have a greater love and affection for a child of that kind, a child in whom he can see the characteristics of the woman whom he loves. You can make mistakes in adoption. There are a great many mistakes. You can make a mistake in a question of artificial insemination. Certainly we are all agreed that no man should be called upon to assume the burden of supporting a child produced in this fashion, or born in this fashion, whom the man does not want to support. If, however, the man comes in willingly and says, "We want children; instead of adopting a child we prefer to have a child; I prefer to have my wife inseminated," I see no reason why in a dozen different ways legislation could not provide for it. After all, it wouldn't even have to be known. Perhaps a certificate filed with the physician, or a certificate recorded would be sufficient under legislation that would say that a child inherits not only if the child is legitimate, but also if the child results from artificial insemination with the consent of the parents.

CHAIRMAN FISHBEIN: I am going to call on Dr. Frederick Falls, head of the Department of Obstetrics and Gynecology of the University of Illinois.

DR. FREDERICK H. FALLS: Like most of the discussants, I have come unprepared to take part in this discussion, and what I have to say has to be extemporaneous. I have done some work with artificial insemination, principally with the use of the husband's semen, and have been disappointed at the results that this particular form of artificial insemination brings. It is quite different from animal experimentation, where you are starting out with healthy animals, a healthy bull, let us say, and a healthy cow, and the semen contains spermatozoa that are capable of fertilizing in the normal way, and this artificial means is used simply to inseminate more cows.

The reason that a couple comes to a physician for artificial insemination is that they have not had children. The difficulty may be with the husband, obviously, but there may be an obvious reason in the wife as well, or one that isn't quite so obvious, and therefore, the results that are to be obtained from artificial insemination in human beings cannot be expected to be as good.

I should like to ask Mr. Wright what the chance of a child that was born following artificial insemination might be to recover damages if, as he grew up, it became known to him that he was a child from such an artificial insemination, and what rights he would have against his own parents. It certainly would not be a comfortable situation to be in.

MR. WRIGHT: I agree with you, doctor, it certainly wouldn't be a comfortable situation to be in, and just what his rights would be, I don't know. There has never been a case of that kind that I know of, but we can analyze it. I doubt if he would have a cause of action. That remains to be seen.

MEMBER: I have been interested in this subject for a good many years. The discussion here has been technical, and legally technical, and has touched the social side and the clinical side of the parents. I got into this work through being interested in sterility, and we had a certain residue of cases that couldn't be relieved in any other way.

I spoke to my legal friends, and they gave me the same answers, practically, and the same problems that have been presented here tonight. We just decided to forget them and take a chance. So we have been taking chances for a great many years. One of my insemination babies was married two years ago. I have not had a chance to inseminate her yet, but maybe I will.

The problem is a very highly emotional one. These couples desire children. When they find out that Mary is all right, and the fault is in John, most often John rises to the occasion and he is willing to go along and not only willing, but he is more than willing. I remember one instance where a man came in first and wanted to know if he couldn't do that. I said, "Have you got a wife?" He said, "Yes." I said, "Bring her in." The thing that bothered him was, he said that everybody had to have a baby carriage to push with something in it.

I have babies of various ages. I have one family where I have three babies who all have different biological fathers. That husband is just as proud of those babies as can be. He takes them to Sunday school, they are smart children, they are better children than the average child is. Why? Because we usually get a very intelligent mother to start with, and our donors are not the scum of the earth. They are the highest type of men, both physically and mentally that we can pick, so that our children produced by this donor's sperm are excellent children.

I realize that all these legal troubles can come up. Maybe they will. I personally keep no records. I haven't a record in the office of any of these cases. Nobody knows a thing about it. You could raid the office, do anything you want, and you can't find a thing.

In regard to the question of race, and all, there you need to know some genetics. You don't want a black in a Greek family. If the family has had blue-eyed blondes for three hundred years, you don't want to show up with a curly-haired, brown-eyed brunette in that family. If you have a black-haired family, or brunettes, the black breeds all black and the first cross is all black, so you don't need to worry. But if you get a blonde family, that has had blondes, you have to get a donor you not only know, but whose genetics you know. He may be a throwback. You want to get a pure-bred blonde to use in a situation like that.

MEMBER: First of all, I want to protest one of the speaker's remarks about these people that have many children just for the pleasure of raising them. We have one every year at our house, and if he thinks it is a pleasure, he can come and keep order during dinner.

I want to concur in what Mr. Wright has said. The doctors say they are ahead of the lawyers, and being ahead of the lawyers, they are being apart from the human race. I think the lawyers are much closer to the people and to

everyday life than the doctor or the scientist, who may do something because it is possible to do or accomplish, and may feel proud that he has done more than could be accomplished by natural means.

Let us assume that one of these doctors who has spoken tonight could produce a baby without either parent. I suppose he would do it, because it would make him outstanding among other doctors, and he would get a certain amount of professional envy. I speak now as a man who is a father of a number of children, and who taught school for some six and a half years. Children are very conservative. They will not forgive any peculiarity, and if you live in a neighborhood where there are many children, it is enough to know that among all of the children, you will be an outcast. Although you may be the prize at a medical meeting, you will be an outcast, if there is anything extraordinary or strange about your ancestry or about your home environment. Anybody raised in a small town knows that. Anybody raised on the South Side of Chicago knows that. Doctors may forget, if they have wealthy patients, or a patient in an exclusive apartment, the effect it is going to have on the child to have no parents. God knows what, after the atomic bomb, they may be able to produce; they may be able to produce through experiment a child without any parents.

You get to this point: In my opinion they have created a hard situation, because women will talk. We all know that. Many of them are going to do it. I don't feel as a lawyer or as a man that any doctor has any right at all to experiment along that line, because the mere fact that a woman wants a child, that she longs for a child, is no reason she should be gratified. I see as much right for an unmarried female to have her desire gratified, as that of a married woman whose husband can't give her a child.

In the Old Testament, Abraham had a child of a bond-woman, but later on was born the child of promise, Isaac was born, and Abraham put away the child of the bond-woman as against the child of promise. I know this, if I know my children from teaching and living with them, you are going to have Ishmael, the outcast. With a normal mother and father it is difficult enough to bring up normal children. I don't see any way that science, outside of one or two cases, can raise a normal child. The promise of the husband, or the present idea of the husband, of course, isn't a sign that he is going to be satisfied with that relation. It is an unnatural relationship for him to be living with a woman with a child that is not his.

I, for one, from my own experience and what I think I know about people, believe that it is a bad situation. There have been ungratified women since Sarah, and I think they might be better ungratified than to bring out children who will be monsters in their feelings and in their relation to other children.

MEMBER: Speaking of protesting remarks, I would like to protest the remarks of the last speaker, my fellow lawyer. I see no moral issue involved here; I see no selfishness involved here at all. I have tonight had confirmed my suspicion that lawyers are the most reactionary people in the world. Why shouldn't a woman who has a natural instinct for motherhood gratify that instinct? Why shouldn't someone born blind attempt to gain sight? Surely those of you who have perfect eyes wouldn't deprive me of the opportunity to wear glasses, so that I may see as well as you. Why, in this field, may not people aspire to obtain what

they cannot have of their own volition. It seems to me that lawyers should affirmatively help in this program. True, the legal problems are most serious, but they can be overcome. They can be overcome, as Dr. Fishbein has pointed out, by statutory means, by legislation. I don't understand the "no, no, no" attitude, merely because it is different.

QUESTION: In successful insemination what percentage of defective children result?

QUESTION: It seems to me the speakers have overlooked an important point, and that is that you can't change people. If the married women want children, they are going to get them. That is one point they have overlooked. I would like Mr. Wright to answer a question. In view of what has been said by fellow lawyers about the moral responsibilities, I can visualize certain communities in this country where actions may be instituted on the grounds that artificial insemination is contrary to public policy, and a doctor could be held criminally liable. I wonder if Mr. Wright has any answer to that problem.

QUESTION: I would like to ask Dr. Greenhill a question. We have been concerned with the childless couple, and attempting to help the couple. Every illustration that I recall that has been brought up has involved a situation where the wife apparently was capable of having a child. Are we to assume that where we find the wife is the one that is incapable, that artificial insemination is not a feasible answer?

QUESTION: We have heard a great deal about Mary being one out of ten, and nothing about John. Suppose Mary has had a hysterectomy and she is sterile, and John is fertile. Suppose John, as the father of a would-be family, is very anxious to have a child. Can he have artificial insemination?

CHAIRMAN FISHBEIN: The speaker means, of course, the transitive use. He means, can he artificially inseminate somebody else, or illegitimately inseminate somebody else?

QUESTION: A prominent man in England, the medical men all know him, who thought he ought to be a father, paid a woman, or agreed to pay her so much money, to raise him a son to take his place in the great world of medicine, and it was successful. She had a child, but it turned out to be a girl, and he refused to pay and was sued in a very prominent lawsuit. I would like to know what recourse he would have; what he could do.

SPEAKER: Mr. Wright has made a very impressive argument on the legal aspects. I think some confusion enters into this problem principally from the standpoint of what the law is now, and others have criticized him on the score of what the law should be. There might be some divergence on it. I find it hard to answer the legal arguments that he has made. It is true that the courts have recognized a legal interest of procreation, as distinguished from intercourse. I recall a New Jersey case where the husband did engage in such relations regularly, but insisted on using a protection or contraceptive, so the wife was deprived of the chance to have offspring, and it went to the courts on the ground that the interest in procreation was an important part of the marital contract. There are cases which hold that undisclosed sterilization in one of the parties to a marriage contract is ground for annulment. In those cases where, for instance, the courts have upheld the right to perform abortions, or to sterilize women, they have also required therapeutic justification, and on the

whole it has been required that the operation be necessary to protect the life or health of the woman.

Another question has arisen here. Suppose the husband was not consulted in regard to this particular transaction? I, personally, find it hard to see why that would not be a crime committed by the doctor. If it is a crime, can the husband, by consent, remove the criminal aspect? In some of the states a doctor who performs a criminal abortion, even with the consent of the woman and at her instance, can be later sued by her for malpractice. There are some very interesting angles there.

I think Mr. Wright made a point which to me is a very scientific point, not just a legal point. He raised the question as to the interest of this unborn child. Frankly, I must express considerable sympathy with that point of view, because the unborn child is subject to a risk that may not be fair; it may be an unfair risk to impose upon a child. I would think that it would be quite dangerous to practice artificial insemination with many consenting fathers agreeable, because if they were of an unstable type, they might later withdraw that approval, and the children then would be in a very undesirable position.

However, it does seem to me that the right of the woman to have a child is an important thing, and the speaker who said that perhaps even unmarried women should have the right to have a child, may be forecasting the future, so far as I know. I think if legislation is passed, it should be of such a character that it would require the full consent of both the husband and wife, of course; that the court, or at least some mechanism would be available for approving the transaction in advance, in a way that would be irrevocable and raise a conclusive presumption in favor of the child, so that that could never be disputed at a later date.

CHAIRMAN FISHBEIN: The Chairman would like to point out that in view of the rise of psychosomatic medicine, it is conceivable that artificial insemination might be a therapeutic procedure.

QUESTION: It was stated here this evening that people want children for pleasure. Schopenhauer said the urge was due to mankind trying to achieve some degree of immortality in this world. One of the things that come to my mind is the case of the maiden lady who would like to have children. She might be financially able to have the children, but if she had them there would be a certain stigma of immorality connected with them.

Another phase that comes to us, and quite practically, is that of the returning soldier, who sometimes finds he has more children than the calendar accounts for. That, of course, has an element of fraud back of it. In order to correct that or control it some way, I direct this question to Mr. Wright: Don't you think it ought to be enacted that whenever a doctor performs a case of artificial insemination he be required to register that act with some official, for two reasons; one, that a fraud can be worked on returning soldiers; secondly, that a woman who has the artificial insemination for the satisfaction of having children, could not be stigmatized as somewhat immoral?

QUESTION: I would like to address a question to Mr. Wright. The discussion here tonight has gone off on a tangent of the morality or immorality of this artificial insemination. I am not at all sure that any group of doctors or lawyers has a right to pass judgment upon people's morality or immorality. Irrespective of that, apparently these doctors and scientists with an experimental turn of

mind have brought into the world a good many thousand children by artificial insemination. What do you suggest, Mr. Wright, that we do about it? Apparently their legitimacy is in question; their property rights are in question. Isn't it high time that as a group of lawyers we make suggestions to the legislature for dealing with the situation that exists, instead of worrying about the morality of the question?

CHAIRMAN FISHBEIN: Before calling on the two contributors to the symposium to close the discussion, the Chairman would like to say that he tries constantly to conceive of medicine as a living and growing science, not static, constantly moving forward and taking account of new knowledge. And I am quite convinced that the vast majority of the leaders in the legal profession like to think also of the law not as a collection of dead statutes and bound-in works of law on the shelves of various law libraries, but they like to think of the law as a living and constantly growing procedure aware of the great changes that take place in the philosophy of man and in our social relationships and attitudes, and in science as well. And I believe that this symposium, which is being held as a joint symposium of the Bar Association and the Institute of Medicine, is evidence that among the leaders of the profession there is this concept of both medicine and law, as living and constantly advancing professions. I will now call on Mr. Wright to close the discussion.

MR. WRIGHT: First of all, I should like to answer the three questions that have been directed toward me. One was regarding a crime against public policy. I think, of course, if anyone abets or aids in the commission of a crime he is an accessory, ordinarily speaking, and I think the doctor would be in that case, too. I think that is a plain and simple answer, without going into it in detail.

With respect to registering the act done by the doctor I think possibly it might be well to register the act not only so that there wouldn't be a fraud on the soldier, but for all reasons that might occur. I see no reason for not registering the act. I think it might be a good suggestion.

One of the speakers said we were dealing with the law as it is, and asking about the moral questions that come up and trying to answer them. I said originally that I didn't have a plan at all, but I did think that if this practice was as prevalent as we are led to believe here tonight, it should be referred to some appropriate committee of the legislature. I did say there should be laws enacted governing the situation. I don't think I am prepared, and I doubt if there is anyone here tonight who is prepared to say what those laws should be, because there should be a study made of the whole situation. As Dr. Fishbein pointed out, a legislative committee has the facilities to go into this, and to call to their meetings men who know about these things and can give facts and figures and testify, and it would be the result of that research which would finally culminate in some law or some legislation. I don't think we could propose any here, but I do believe that the time is ripe for considering some legislation. What it shall be must be a result of study.

CHAIRMAN FISHBEIN: Dr. Greenhill, may we have your closing discussion?

DR. GREENHILL: When the chairman of the committee asked me to present this subject I said, "No, decidedly no," and when he repeated his solicitation I continued to say no, and I gave him two reasons: First, I was pressed for time and, second, the subject was not one to be discussed

in an open meeting of this kind. I said that this subject should be discussed by 20 or 25 lawyers, the same number of physicians and perhaps the same number of ministers. Then perhaps some definite conclusions could be deduced.

The meeting has been held here, I presented my paper and you have heard a great deal of discussion. The morality angle was emphasized by a number of speakers.

First, let me answer a question directed to me concerning the incidence of fetal monstrosities and congenital deformities following artificial insemination. The incidence of deformities found in early miscarriages is enormous, almost 50 per cent. The incidence of deformities at birth is 1 per cent. To the question of how many monsters I personally have delivered or seen in my own cases following artificial insemination may I say that the answer is none. However, I have not as yet delivered 100 babies for women whom I have inseminated. I believe the incidence of deformities will surely not be higher than that for babies born as a result of sexual intercourse. It may be less because we select the donors and we choose the women to be inseminated. In Seymour and Koerner's series the incidence of defective babies was extremely low.

The matter of adoption was brought up. Personally I see no need for adoption because the men who come to us want the matter kept secret. In spite of what one of the speakers says I do not know of a single woman who was inseminated who ever spoke about it. Not a single one of my patients has even told her own parents about being artificially inseminated so that even women who usually talk about everything do not mention their babies obtained by artificial insemination. Therefore no one in the neighborhood, be it the South Side or elsewhere, can find out about such babies. No baby has any stigma attached to it because its father is unknown. The husband certainly will not tell because it would reflect on his manhood. If a couple legally adopted a child born after artificial insemination anyone could see the adoption proceedings. As I said that is just what the couples in question do not want. They do not want anyone to know that the baby is not entirely their own.

The second angle, of course, is this: If the truth became known or if the husband legitimized the baby, a lot of cackling women would assume that the mother of the child had had intercourse with someone else and that the husband was a liberal fellow and adopted the baby as his own.

Dr. Koerner pointed out an extremely important aspect; namely, that about 10 per cent of married couples in this country—and it is about the same all over the world—do not have babies, not because they do not want them, but because they cannot have them. This is very sad. Women married to impotent men have as much right to have normal, healthy babies as those whose husbands are potent.

A physician should have a heart-to-heart talk with couples who desire artificial insemination and select only a few at a time. If I were to take all such patients who come to me I would not have time to be here tonight. That is true of all specialists in this line of endeavor. I do not know what the incidence is of the couples I accept but it is extremely low. After the talk I try to decide on the basis of the morals of the people concerned, their education and their health. Although financial stability is important it should not play too great a role because we all know that there are plenty of poor people who raise children properly, and many rich people who are failures at rearing children.

This meeting was arranged with the idea of trying to secure laws to justify the procedure of artificial insemination and to protect all of us who are involved; namely, the physician, the husband, the wife, the donor and the child. Mr. Wright said that we (meaning the lawyers) do not know what to do with the cases of artificial insemination. Regardless of what you lawyers believe unless you take some action artificial insemination will continue. The last speaker brought up an important question: What are you going to do with the children who are already here as the result of artificial insemination? The fact that so far as we know there is no instance in which a judge specifically handled a case for which he could lay down a law (not *dicta*) about artificial insemination proves one thing—that the people who are artificially inseminated keep their mouths shut and are happy. Of the thousands of artificial inseminations that have been conducted in the country apparently not a single couple has gone to court or there would be some case you men could cite from now until doomsday, like the citation of 1891. Here we are more than fifty years later and Mr. Wright still cites the 1891 definition of adultery. Certainly the definition concerning the matter of giving up the right to have a child has no bearing in the definition of adultery. Some women have intercourse extramaritally and use contraceptives to prevent pregnancy. Certainly this is adultery. The matter of having a child does not enter into the question of adultery.

I should like to take up some of the remarks made from the floor. One speaker facetiously mentioned the case of a couple in which the wife is barren, let us say that she has

no uterus, and the husband would like a child. If the husband is adamant about it he will try to obtain a divorce, because he knows that the only way he can have his own child would be by marrying someone else. Yet I have had a man come to me with a request for me to select a girl or woman who would for a specified sum of money carry his baby. The wife was willing to have this done; the sum was to be a large one and immediately after the birth of the child legal papers would be drawn up giving the child to the father and his wife. This is another type of case to complicate the law. I have been doing artificial insemination for many years. I mentioned the fact that my first successful case took place in 1923. When I had the temerity to tell Dr. DeLee about that he censured me severely and I tore up my records. However, I continued to do artificial inseminations, and as time went on I performed more and more of them but I never wrote a paper on this subject. When *Time Magazine*, *Reader's Digest* and the *Chicago Tribune* gave publicity to artificial insemination, I, like many other specialists, was besieged by a large number of couples.

I believe artificial insemination is a humanitarian procedure. If you could see the real pleasure of these couples when they have a baby, I am sure you would agree that they have as much right to that happiness as anyone else. In closing I make a plea to you lawyers to tell us physicians whether artificial insemination is legal or illegal. If it is illegal we shall stop this procedure. If it is legal or you give us no opinion, we shall continue to help bring happiness to the couples who desire and are worthy of it.

### Oliver Wendell Holmes on Puerperal Fever

The practical point to be illustrated is the following: The disease known as puerperal fever is so far contagious as to be frequently carried from patient to patient by physicians and nurses. . . .

1. It is granted that all the forms of what is called puerperal fever may not be, and probably are not, equally contagious or infectious. . . .

2. I shall not enter into any dispute about the particular mode of infection, whether it be by the atmosphere the physician carries about him into the sick-chamber, or by the direct application of the virus to the absorbing surfaces with which his hand comes in contact. Many facts and opinions are in favor of each of these modes of transmission. But it is obvious that, in the majority of cases, it must be impossible to decide by which of these channels the disease is conveyed, from the nature of the intercourse between the physician and patient.

3. It is not pretended that the contagion of puerperal fever must always be followed by the disease. It is true of all contagious diseases that they frequently spare those who appear to be fully submitted to their influence. Even the vaccinia virus, fresh from the subject, fails every day to produce its effect,

though every precaution is taken to insure its action. This is still more remarkably the case with scarlet fever, and some other diseases.

4. It is granted that the disease may be produced and variously modified by many causes besides contagion, and more especially by epidemic and endemic influences. But this is not peculiar to the diseases in question. There is no doubt that smallpox is propagated to a great extent by contagion, yet it goes through the same period of periodical increase and diminution which have been remarked in puerperal fever. . . .

5. I take it for granted that, if it can be shown that great numbers of lives have been and are sacrificed to ignorance or blindness on this point, no other error of which physicians or nurses may be occasionally suspected will be alleged in palliation of this; but that whenever and wherever they can be shown to carry disease and death instead of health and safety, the common instincts of humanity will silence every attempt to explain away their responsibility.

—From *The New England Quarterly Journal for Medicine and Surgery*, 1843.

# Diagnosis and Treatment of Cancer of the Uterus\*

H. DABNEY KERR, M.D.

IOWA CITY, IOWA

*Too many carcinomas of the uterus still go undiagnosed in the early stages. This has been reiterated by the author as it must be from time to time. A brief survey of the essential concepts in recognition and treatment of this disease.*

If it were not for the fact that carcinomas of the cervix and body of the uterus are such common diseases, so relatively easily controlled when diagnosed early, so deadly when seen late and withal so accessible to early detection to almost any practitioner of medicine, I would not have the temerity to take up your time with a further discussion of the subject. However, the condition is so common and yet so uniformly fatal when diagnosed late or treated improperly that I welcome the opportunity to bring it to your attention again.

For the purpose of this discussion it may be well to consider carcinoma of the cervix first and this can be considered under five main headings: (1) incidence, (2) etiology, (3) symptomatology, (4) pathology and (5) treatment. Most of what I shall say about the cervix can in general be applied to the corpus as well.

## INCIDENCE

Statisticians are not in complete agreement as to whether carcinoma of the cervix is first in the entire group of malignant tumors or whether it is outnumbered by carcinoma of the stomach. It is certainly first of neoplasms in women, however, and comprised 29 per cent of 31,000 cases of carcinoma in one series. This alone should make it a condition worthy of repeated discussion and emphasis.

Carcinoma of the cervix makes up about 89 per cent of the malignant tumors of the uterus, the other 11 per cent being in the body. It occurs most frequently between 40 and 50 years, but it may be found in the aged or youthful, but let no one be lulled into a false sense of security by the fact that the patient with suspicious symptoms is in her thirties, her twenties or even younger. The youngest patient we have seen with proved carcinoma of the cervix was only 17

years old. If anything, it is even more important to recognize the condition in the young because the disease tends to progress more rapidly and to invade faster in the youthful.

## ETIOLOGY

The etiology of carcinoma of the cervix has a definite relationship to lacerations incident to childbirth and with the irritation and infection that usually follows. A careful study indicates that one birth is as effective in producing the usual conditions as multiple ones, but that does not mean that nulliparous women are entirely free from danger. They seem to be in relative safety, however. Endocervicitis and cervical erosions also seem to play a part in the etiology. This has further substantiation in the fact that the cervix is a common site for squamous metaplasia, due probably to the constant process of injury and repair that goes on in this region. It is relatively easy to see how this might lead to abnormal cell divisions and the development of neoplasm. A history of leukorrhea can almost always be obtained but the relationship of this condition, as well as of leukoplakia to the onset of cancer is not too clear.

## SYMPTOMATOLOGY

Someone has made the trite remark that to make a diagnosis, one must think of the condition. This is nowhere more true than in carcinoma of the uterus. If one thinks of the possibility of cancer, the rest is comparatively easy. In its earliest stages, carcinoma of the cervix produces no symptoms because there is no ulceration. Practically speaking, the cardinal symptoms of discharge and bleeding are dependent on ulceration of the mucous membrane. Up to the time of ulceration the patient will not seek medical aid because she is asymptomatic and if her doctor were making a periodic examination, he might well miss the lesion because of this lack of superficial change. All hope of making an early diagnosis need not be given up, however, because the lesion is still early when ulceration first occurs—and at that time there are symptoms and changes which the physician can find.

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Read before the meeting of the Indiana State Medical Association at Indianapolis, October 30, 1946.



I wish to emphasize at this point that the old textbook symptom of a foul, watery, vaginal discharge is usually indicative of a late stage of the disease where almost all hope of successful treatment has passed.

If we are to make any advance in the results of the treatment of this condition, we *must* make earlier diagnoses. To do this requires work along two lines: (1) lay education and (2) professional education. The American Cancer Society is working on the first part of the problem, but it is up to us to put our own house in order. We, too, can do our part in lay education by constantly impressing our feminine patients with the fact that irregularity of menses, intermenstrual bleeding, contact bleeding, etc., must not be taken as evidence of physiologic change, as is usually assumed by well-meaning but poorly informed and sometimes meddlesome friends and neighbors. If we can break this vicious chain of misinformation, we will have cleared up the first of the two major obstacles to early diagnosis of cervical cancer. When it comes to the medical profession, it is shocking to find patients with symptoms at least consistent with carcinoma on whom a pelvic examination has never been done. But this happens all too frequently and sometimes by usually conscientious but harassed doctors. Those of us who are connected with teaching institutions must see to it that our students are made cancer-conscious, particularly regarding the disease in this site. Those of us who have graduated, but I trust not finished our medical education must redevelop, if we already have lost, our interest in, and wholesome respect and fear for malignant disease. In no other field does alertness yield such high returns. To examine a woman for a suspected lesion of the cervix requires only a pelvic examination and a biopsy in suspicious cases. It is not much of a procedure to do a biopsy and to suspect the carcinoma is of paramount importance. If one is hesitant about doing the biopsy the patient can always be referred to a surgeon or gynecologist. The use of the cytologic vaginal or cervical smear is becoming more and more recognized as a valuable ancillary method in the diagnosis of carcinoma of the uterus—both cervix and corpus—and in the hands of the pathologist trained in this type of examination, it may prove to be of primary importance.

Intermenstrual bleeding or persistent discharge should always be an indication for a pelvic examination. As a matter of fact, this should always be included in any complete physical examination. An example of what I mean is illustrated by the following. A nervous woman had a fainting spell—the kind that could wait until she was able to call her daughter-in-law who worked for a doctor. When the doctor

saw her, he suggested she might be anemic but blood studies showed this was not the case. A complete physical examination was made and an early carcinoma of the cervix was found. If this man had been satisfied with a routine, incomplete examination which does not include a pelvic examination, this woman's chances of a cure would have been largely lost. Some of you have undoubtedly had similar experiences and the chances of a "cure" in these cases is greatly enhanced.

In the earliest stages of carcinoma of the cervix, as noted above, there are no symptoms, the microscopic changes in the mucous membrane are slight, and consist only of erratic mitoses, loss of polarity, crowding of the cells, abnormal staining characteristics, etc. But these are the changes that confront and concern the pathologist primarily and are his responsibility. We must rely on him to tell us whether a carcinoma is present or not, what grade it is and what the cell type. In the earliest cases it is especially important to work closely with the pathologist in trying to work out the best plan of treatment for the patient. Carcinoma "in situ" may reasonably have different therapy than one with a gross tumor. Our responsibility as front line doctors is to lose no opportunity of adequately examining a woman who comes to us because of abnormal bleeding or discharge. On us devolves the task of telling her that everything is all right or of determining by inspection and palpation that she has a suspicious or definite lesion and to be prepared to do a biopsy or send her to someone who will do one.

## PATHOLOGY

About 95 per cent of carcinomas of the cervix are epidermoid or squamous cell while the other five per cent are adenocarcinomas. As far as prognosis is concerned, however, in our experience there is no essential difference. One seems to respond to treatment about as well as the other. As carcinoma of the cervix extends, it may grow superficially and form an exophytic or everting mass, or it may invade and destroy the deeper tissues, ulcerate and become endophytic or inverting. A superficial lesion may develop into either type, as may one originating in the cervical canal. Bulky tumors may fill the vagina while the ulcerating type may destroy the entire cervix and penetrate into the bladder or rectum.

Cervical carcinoma spreads by: (1) direct extension, (2) lymphatics, (3) blood stream, or (4) implantation. Lymphatic spread usually occurs late, after involvement of the parametrium. In a series of 60 cases, Wertheim found 15 per cent lymphatic spread in early



cases and 31.7 per cent of all cases. Blood stream spread is late and infrequent, 2.5 per cent, and implantation is usually the result of ill-advised and poorly performed surgical procedures.

The diagnosis of carcinoma of the cervix does not depend upon the clinical grouping but the grouping does allow one to have a better idea of the prognosis. Two methods of grouping in use are: (1) Schmitz and (2) League of Nations. According to Schmitz, group or stage I is a lesion not larger than one cm. which is confined to one lip of the cervix, group II is still confined to the cervix with no involvement of the parametrium, group III has extended into either side of the parametrium without a frozen pelvis but with some limited mobility of the cervix while group IV shows (1) extension to the pelvic wall with fixation of the uterus, (2) extension to the bladder or rectum, (3) extension down the vagina and (4) distant metastases, and to these we have added yet another, i.e., recurrence, after either surgery or radiation. The League classification of group I includes Schmitz I and II while Schmitz III is divided into II and III of the League.

The diagnosis of any except the earliest lesions can usually be made clinically, but it is always advisable to have histologic proof. We were saved in one case which, though it looked like carcinoma, was proved to be tuberculosis. It is not satisfactory to rely on Schiller's test, in which the cervix is painted with Lugol's solution, because other conditions than cancer give a positive test. Diagnosis by the Panpanicolaou test or vaginal cytologic smear is undoubtedly of value in the detection of unsuspected and asymptomatic cases, but it is probably not so generally applicable as biopsy at present.

The question of histologic grading of cervical tumors is important for a more complete understanding of these lesions, but for the purpose at hand, it is sufficient to recall to mind what all of you undoubtedly know and that is that the grade IV is the most anaplastic, most infiltrating and most rapidly growing of these lesions while grade I is the most differentiated. In making the diagnosis, this does not specifically concern us, except as an indication of treatment, for grade IV responds better to irradiation and more poorly to surgery.

### TREATMENT

Having now made a diagnosis of carcinoma of the cervix, what treatment is to be advised? One cannot give a categorical answer but generally speaking, it should be by irradiation. Historically, the first successful attack on this condition was surgical but it

could be used in only the earliest cases. It was, however, a definite advance in the treatment of this condition. For the past 25 years or more it has become increasingly evident that more can be accomplished by roentgen and radium radiation because all cases can be treated regardless of the extent or character of the primary lesion. In the *proper hands* and with carefully selected cases, surgery is a satisfactory method of treatment. However, in addressing a group of mature doctors such as I find here today, it is not so necessary to be categorical as it is to present the facts.

Lynch has this to say about the selection of cases for operative attack on cervical carcinoma: "Surgery should be reserved for the treatment only of patients whose cancers are limited definitely to the cervix and who themselves are first class surgical risks by reason of age and general physical condition. The cancer should be completely operable in the sense that the surgeon can remove both the primary growth and the adjacent regions which might have microscopic extensions. The ulcer at the time of operation should not suggest active infection. The candidate should be young enough to have a presumptive survival of at least ten to fifteen years after radical operation. The old, the fat, the potential cardiovascular case, the diabetic, women with asthma or with blood so low that it can be built up to normal only by repeated blood transfusions or even patients whose brachial veins are deep set and not readily available for transfusions are not suitable for operation. Such patients can be treated much better by radium and high voltage roentgen rays."

It is important to bear in mind that the extent of microscopic infiltration beyond the primary site cannot be determined and that the surgeon who does a limited operation fails in his duty to the patient.

Lynch then goes on to say, "The field for surgery in the treatment of cervical carcinoma is restricted by the greatly improved results now obtained by radium and high voltage roentgen rays."

It must be remembered that there is great selection of cases when operation is contemplated and that even then the relative cure rate is just about the same as for irradiation. But irradiation excludes no case from its statistics. One must also consider that irradiation mortality will be not more than two per cent, while in stage II, which is the most advanced operable group, the operative mortality may be above 20 per cent. It is safe to say that good irradiation is always as good as the best surgery in comparable stages of the disease and has the advantage of no selection. Practically all cases are treated.

However, I do not decry the use of surgery in the hands of experienced pelvic surgeons in well selected cases, but I do aver that much of the so-called surgery done by self-styled surgeons on patients with carcinoma of the cervix should never have been attempted. When one has seen, as I have, simple amputation of the cervix, conization of the cervix in advanced cases and even supravaginal hysterectomy with the cervix left in place in carcinoma of the cervix, it is enough to make one tremble for the patients and for the profession. The most charitable thing one can say in these instances is that the surgeon was mistaken regarding the extent of the lesion or in his surgical ability. In many cases, much more damning criticism could be made.

It is, of course, just as reprehensible for an untrained man with an x-ray machine or rented radium to treat these lesions because he, too, will almost surely cause the patient to lose whatever chance she had through improper treatment. Owning an x-ray machine in itself, no more makes a man competent to use it, than having a fine set of surgical instruments makes a man a good surgeon.

Having made a positive diagnosis of carcinoma of the cervix and instituted proper treatment, what results can we expect? Generally speaking, with radiation, stage I has in the neighborhood of 90 per cent five-year survivals, stage II, 60 per cent, stage III, 30 per cent and stage IV, practically none.

It is interesting and exceedingly important to look at these figures in the light of the effect of delay in making a diagnosis. A stage I case can easily become a stage II or even a stage III in 30 days and a stage II may easily become a stage III or stage IV in the same length of time. At this rate, a patient loses from one to two per cent chance per day. That is a great responsibility for the doctor who advises the patient with bleeding or with a discharge to take douches for a month or six weeks and then come back if she still has trouble. Many women are thus condemned without a chance. One should never send such a patient home with douches, hormones, vitamins or only reassurance, unless there is sound basis for it. And that can be found only after a careful pelvic examination with a biopsy or diagnostic curettage. Sight should never be lost of the fact that carcinoma is an implacable foe and that, whereas we may sleep, the neoplasm never does. Thus, we are challenged day and night.

The movement on foot to establish detection clinics for uterine neoplasm is well under way and should aid materially in bringing to light early cases. Here the Panpanicolaou test or vaginal cytologic smear referred to above aided in the diagnosis of 193 unsus-

pected carcinomas of the uterus or lower genital tract and is a valuable adjunct to early diagnosis.

Periodic examinations may be valuable, but I am sure that they are not the final answer to our aim of making early diagnoses. This can only be done by educating women to look for advice when there are symptoms and the profession to always suspect cancer.

Just a word about radiation for uterine cancer: Many people, unfortunately, medically trained men among them, think that because the roentgen rays cannot be felt and cause no immediate reaction except nausea (which most patients are led by the referring physician to expect without fail), many, I say, think that irradiation is a simple procedure and should cause no reactions. Let me say, however, that irradiation for carcinoma is a major procedure that may carry a slight mortality and considerable morbidity, such as skin damage, bowel irritation, irreparable damage to the colon perhaps necessitating colostomy, damage to the pelvic bones and even fracture of the femoral neck. We have already had 16 such femoral fractures. These changes, however, should not deter the well-trained radiologist from doing all he can for these patients. After all, the surgeon expects up to 20 per cent or more mortality but the public has been educated to expect or tolerate the worst with surgery.

Practically everything we have discussed regarding the need of the early detection of carcinoma of the cervix can be said regarding cancer of the corpus. The symptoms are relatively the same but patients with corpus carcinoma are usually in the postmenopausal period. Many of them complain that they have begun to menstruate again. In all such cases, the only safe procedure is a diagnostic curettage with careful histologic examination of the curettings. Vaginal smears for neoplastic cells may be of considerable aid in the detection clinics.

Carcinoma of the fundus is almost always adenocarcinoma, although occasionally there are cases of squamous metaplasia. The grades of the malignancy are stated as I, II, III, and IV, where grade I is the differentiated type or adenoma malignum. The more anaplastic tumors are prone to invade the muscularis earlier and spread to the parametrium.

The treatment of fundic carcinoma is usually surgical, with or without pre-operative radium treatment. We prefer to give radium and follow this in about six weeks by total hysterectomy. Only those patients who by reason of their physical condition or the advanced stage of their disease are considered inoperable, are treated by irradiation alone. If the process has extended beyond the muscularis of the uterus, it is obvious that radium cannot sufficiently influence it.

In summary then, let me reiterate (1) carcinoma of the uterus is a common type of neoplasm, (2) its symptomatology is such as to arouse the suspicions of any thoughtful doctor (and we hope soon, layman), (3) its detection is relatively simple, once the possibility is thought of, (4) as a general statement, the best treatment is by irradiation in lesions of the cervix and by a combination of radium and surgery in lesions of the fundus, and (5) incomplete surgical or radiation methods are to be condemned.

I would like to conclude with an anecdote. A professor of gynecology was asked to talk to a medical society on the subject of carcinoma of the cervix—its

diagnosis and treatment. Being very earnest and methodical, he expounded the symptoms again and again, outlined the pathologic findings, stressed the need for earlier diagnosis, told how it might be obtained and affirmed that in our hospital, irradiation was considered the best treatment. Then he wound up with a good summary and more emphasis on all the above mentioned points. After the applause had died down and the group was dispersing a doctor from the audience came up to him and said, "Dr. X, I have a woman about 45 years old who has had some bleeding between her periods. What do you think I ought to do about it."

### Veterans Administration Home-Town Medical Care Program

Dr. Paul R. Hawley, medical director of Veterans Administration, recently explained the extent of the medical services which may be rendered to veterans under VA's home-town medical care program.

Under existing legislation, veterans may be furnished out-patient medical or dental treatment in VA clinics, in private offices of physicians or dentists or in their own homes *only for disabilities recognized by VA as incurred or aggravated in line of duty in active service*, Dr. Hawley emphasized.

He added that only prescriptions for service-connected disabilities may be filled at government expense by local pharmacies under VA's home-town prescription service.

The medical facilities of VA regional and sub-regional offices, clinics and hospitals, under law must be utilized to the fullest extent for examination and out-patient treatment of veterans.

When determining whether a veteran, residing in an area where there is a VA field station (clinic, hospital, etc.), is to be referred to a VA clinic or to a civilian physician, the best interests of both the veteran and the government will be considered.

Although VA medical facilities must be utilized to their fullest extent, this does not mean that veterans will arbitrarily be ordered to field stations.

If veterans establish to the satisfaction of the chief medical officer of a VA regional office that reporting to a field station would work unnecessary physical hardship or cause excessive loss of time from employment, fee-basis doctors may be utilized. In any event, final decision rests with chief medical officers of VA regional offices.

Then too, when the backlog of physical examinations justifies or when out-patient treatment is not being rendered expeditiously, the chief medical officers of VA regional offices may utilize the services of civilian physicians working under state-wide contracts with VA.

Male veterans may be admitted to private hospitals (preferably those under contract by VA) for in-patient treatment of *service-connected* disabilities by civilian physicians under contract to VA only if their condition is such as to constitute an emergency which cannot be met by a VA hospital because of the lack of beds or because the patient's condition prohibits travel.

Prior authorization for this hospitalization and treatment in a private hospital must be obtained by letter, telephone or telegraph. If, owing to the extreme emergency of the case, prior authorization is not obtained, the physician or admitting hospital should notify VA within 72 hours. If the facts so warrant, VA will then issue authority for the veteran's private hospitalization and treatment.

Women war veterans may be admitted to private hospitals (preferably those under contract by VA) for in-patient treatment of *both service-connected and nonservice-connected disabilities* by civilian physicians if it is an emergency which cannot be met by VA or because of the unavailability of beds or because the serious condition of the patient precludes travel. Authorization must be obtained exactly as in the case of male veterans.

# The Differential Diagnosis of Aortic Stenosis, Pulmonary Stenosis, Patent Ductus Arteriosus and Coarctation of the Aorta\*

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*It is refreshing to read again of the importance and application of the old methods of examination—inspection, palpation, percussion and auscultation. Though the x-ray and the electrocardiogram may be helpful aids, when all is said and done, the diagnosis of valvular heart disease and of certain anatomic anomalies depends on fundamentals of physical diagnosis.*

The classical methods of physical examination of the heart and blood vessels are being neglected today as a result of the introduction of roentgenographic and other technical methods of exploration. Many clinicians are now aware, however, that the size and shape of the heart as revealed by fluoroscopic and roentgenographic methods are of minimal value in diagnosis in many patients. Electrocardiographic tracings are of limited value in studying the functions of the circulatory system.

It is my purpose to indicate how four clinical diagnoses can be accurately differentiated on the basis of knowledge of the dynamics of the circulation and the proper use of methods used in physical examination, namely, inspection, palpation, percussion and auscultation. The last of these methods, *auscultation*, is of the greatest value.

It is well known that if an elastic tube or channel in which liquid is flowing is partially compressed or constricted mechanically at some point, there will be turbulence set up in the liquid. On palpation this turbulence will be noted as vibrations of the wall which we designate as thrill. On auscultation a murmur will be heard. The thrill and murmur are propagated in the direction of the flowing current but they will also be propagated backward against the current but not to so great a distance as those which appear beyond the point of constriction. If we now introduce into the elastic system an eccentric pump made so that the pulse wave is simulated, it can be shown that the thrill and murmur travel on the

pulse wave and not as sound waves. The rate of travel coincides with the rate the pulse wave travels which may be only one-hundredth as rapid as the speed of sound in liquids. Recent unpublished studies by Dr. William F. Hamilton<sup>1</sup> of the University of Georgia indicate that in animals the rate of propagation of the pulse wave increases as the periphery is approached and that the diastolic pressure determines the rate of its propagation. Levine<sup>2</sup> suggested that murmurs in aortic stenosis were transmitted to distant points through the bones of the extremities. Inspection of his phonocardiographic tracings indicates that the time relations would be highly improbable if the vibrations were transmitted by bone in view of the extreme rapidity of travel of sound waves in bone or other solid objects. It is almost certain that the vibrations were carried on the pulse waves.

## AORTIC STENOSIS

This pathologic condition may serve as a good example to demonstrate the use of physical signs in establishing the diagnosis.

*Inspection* may show that the patient has pallor to a varying degree depending upon the severity of the constriction at the aortic valve. The apical impulse may be displaced downward and outward from the midclavicular line.

*Palpation* may show a plateau pulse but if the usual aortic insufficiency is present the plateau pulse may be minimal or not clearly discernible where the insufficiency is dominant. The systolic blood pressure, or the pulse pressure, or both, may be below normal unless aortic insufficiency predominates. A thrill may be felt over the aortic valve and extending into the neck and beyond, along the course of the great vessels. It is usually of greatest magnitude in the second right intercostal space adjacent to the right sternal border unless the heart and great vessels are displaced. This thrill is generally designated as systolic but it coincides with the apex impulse only over the base of the aorta. At any point distal to this area

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the thrill appears later than the apex impulse and over the carotid artery the thrill is approximately 1/20 of a second after the apex impulse or the first sound at the apex. When audible at more remote points along the larger systemic arteries the thrill is further delayed. This is due to the fact that the thrill travels on the pulse wave and not as sound. The thrill may also be felt at the apex in which case it has been propagated backward in the left ventricle and it appears later than at the base of the aorta. *In most advanced cases of aortic stenosis there may be no systolic thrill or murmur over the base of the aorta or over the major systemic arteries.* The author has observed three such examples. It would appear that the turbulence and the pulse wave in such cases are reduced to such a marked degree that a thrill and murmur are imperceptible.

On *percussion* the left border of the heart may be displaced to the left and downward. If other valvular abnormalities exist, other displacements may be noted in addition to those mentioned.

*Auscultation* shows time relations with respect to the murmur which are peculiar to the thrill. The rough murmur is systolic in time, i.e. it coincides with the apex impulse and the first sound at the apex. The murmur heard at the base of the aorta (in the second intercostal space adjacent to the right sternal border) coincides with the first sound and is synchronous with the thrill. At points distal along the great vessels of the systemic circulation the murmur is progressively remote in time. At the carotid artery the murmur appears approximately 1/20 of a second after the apex impulse and coincides with the pulse wave at the carotid artery and the thrill, if present. At more distant points the murmur is still later. At the apex one may hear a systolic murmur in such cases. This murmur is also delayed and in uncomplicated cases it is evident that this murmur has been propagated from the aortic valve through the blood in the left ventricle. Since the right ventricle overlies the left ventricle except at the apex and the left border, this murmur is obscured over all of the heart except at the apex which lies close to the wall of the chest. The sphygmophone<sup>2</sup> may be used to determine the timing of the murmurs at the different points and to analyze lesser degrees of variation. Also by palpating the systolic impulse at the apex and listening to the murmur along the course of the aorta and its branches the difference in timing of the murmur may be readily determined.

#### PULMONARY STENOSIS

The principles outlined for aortic stenosis apply equally in pulmonary stenosis. The constriction may

be so great that some of the physical signs may not be noted. This lesion is seldom observed alone and is generally complicated by other congenital anomalies. In acute endocarditis the pulmonary valve may be constricted by vegetations.

*Inspection* generally shows varying degrees of cyanosis and so-called pulmonary osteo-arthritis. The nail beds may show enormous vascular loops especially under the convex dome of the nails.

On *palpation* there is a rough systolic thrill which is propagated over the upper part of the chest on the left particularly, but it may be felt also in a semicircular area centering at the second right intercostal space adjacent to the sternum. This thrill is not propagated beyond the chest. At points distal to the pulmonary valve the timing of the thrill is later than at the point of origin.

*Percussion* and roentgenographic studies may show displacement of the right border outward and enlargement of the right auricle. Electrocardiograms may help to differentiate right from left ventricular preponderance often seen in aortic stenosis but such methods are of only supplemental value. Associated lesions in either case may modify the roentgenographic or electrocardiographic findings.

On *auscultation* a rough and generally loud systolic murmur is heard in the second left intercostal space adjacent to the sternum. As one observes this murmur over the chest at points more distant from the pulmonary valve, either by the use of the sphygmophone, or by comparison with the apical impulse on palpation, it is apparent that the time of appearance of the murmur is delayed at these more distant points. When the murmur is heard in the upper part of the chest on the right, the differences in timing are considerable because the pulse wave travels a greater distance. The murmur over this area is of lessened intensity because the right pulmonary artery passes behind the ascending aorta and thus is more deeply placed in the thorax.

#### PATENT DUCTUS ARTERIOSUS

This congenital defect is now of unusual interest because in its uncomplicated form, patients can be benefited by surgical methods. Therefore, the hazards of myocardial failure or infectious processes may be avoided later in life.

*Inspection* may show no abnormalities unless myocardial failure has supervened. In extreme examples the systemic arteries at the base of the neck may pulsate markedly. Over the upper part of the chest on the left, anteriorly, one may observe abnormal pulsa-

tions. There may be clubbing and cyanosis if there are associated lesions. In older persons in whom the ductus arteriosus has become obliterated by atherosclerosis (three cases from personal experience) there may be extreme cyanosis and polycythemia associated with marked atherosclerosis of the branches of the pulmonary artery.

*Palpation* generally shows a marked rough thrill over the second and third left intercostal space adjacent to the sternum and the thrill may be widely felt over the ventral surface of the thorax. If one compares the timing of this thrill with the systolic impulse at the apex it will be noted that the thrill appears at least one-tenth of a second after the apex impulse. The pulse pressure may be high and the pulse of the water-hammer type in cases of long standing or in those with a large fistulous opening.

On *percussion* one may find dullness in the region of the pulmonary conus and the enlargement of the heart both to the left and right. Enlargement may be confirmed by roentgenographic methods and the "hilar dance" may be noted especially in those patients who have a fistula of some magnitude.

*Auscultation*, when carefully done, will reveal findings which may be considered pathognomonic due to the dynamic conditions existing in this malady. Contrary to what is stated in books on physical diagnosis, the accentuated part of this murmur is not, strictly speaking, systolic in time, i.e., it does not coincide with the first sound at the apex. In most examples there is a continuous murmur, often machinery-like in quality during the phase which most clinicians call the systolic phase. In patients in whom the fistulous opening is large, the murmur may be coarse and of low intensity. It can readily be demonstrated that the accentuated phase, when present, appears approximately one-tenth of a second or more after the apex beat or the first sound at the apex. This murmur is not transmitted beyond the chest because it originates in the pulmonary artery after the pulse wave from the aorta has spread to the pulmonary artery. The accentuated phase does not appear until the pulse wave has traversed the aorta and passed through the fistula. This accounts for the delay in timing which is so characteristic of the "systolic" phase of this murmur. The less intense phase of the continuous murmur can probably be explained on the turbulence set up in the pulmonary artery because aortic blood continues to flow into the pulmonary artery throughout the cardiac cycle. The differences in time relations may be further described and may be readily verified. By the use of the symphonophone or by a combination of auscultatory and

palpatory methods it can be demonstrated that the "systolic" accentuation of the continuous murmur at the pulmonic area appears later than the pulsation in the abdominal aorta and even in the femoral artery. This offers clear evidence that the chief or loudest component of the characteristic murmur originates in the pulmonary artery.

### COARCTATION OF THE AORTA

This congenital anomaly is more common than is generally supposed. About 4 per cent of all patients with marked hypertension in the arms are subject to this defect in the thoracic aorta; a lesser percentage show atresia of the ascending thoracic aorta or of the abdominal aorta. Of chief interest at this time is the opportunity to cure such patients by surgical means. It is probable that treatment should be undertaken at an early age to insure success. It is, therefore, urgent that a diagnosis be established early in life if possible.

*Inspection* generally shows prominent pulsations in the carotid arteries and sometimes the innominate and the subclavian artery or arteries are seen to be pulsating vigorously. The arteries surrounding the scapulae and occasionally the intercostal arteries are observed to pulsate.

However, *palpation* is more likely to show pulsation of arteries in the region of the shoulder girdle or over the chest. The pulse may be bounding or of the water-hammer type as seen in high pulse pressure, which is confirmed by the blood pressure readings in the arms. In the abdominal aorta pulsations are frequently diminished or absent and the femoral pulsations may be reduced in volume. Blood pressure and pulsations in the lower extremities are generally found to be reduced or may be absent on cursory examination. The time of the appearance of pulsations in the femoral arteries or beyond is greatly delayed in marked cases when compared to the radial pulse or with the normal difference taken from the first sound at the apex. A thrill may be felt over the left upper thorax or in the region of the left clavicle and, if found, it coincides in time with the murmur. The left subclavian artery may be anomalous or variable and the left radial pulse may be of reduced volume.

*Percussion* may show enlargement of the heart as in hypertension.

*Roentgenographic* studies may help in demonstrating an enlargement and rotation of the aorta and the absence of the usual shadow of the descending limb of the thoracic aorta, although in young individuals the lack of the shadow of the thoracic aorta would not be of diagnostic value. The serration or scalloping of the inferior dorsal shafts of the ribs may be striking.

*Auscultation* is of importance in classifying this lesion. The murmur is heard chiefly over the left upper part of the dorsal chest on the left. It is generally of greatest intensity over the first and second thoracic vertebrae and over the left thorax adjacent to these vertebrae, although it may be heard more widely, even in the region of the left clavicle, and fading off from these areas. This murmur is said also to be systolic in time but it begins distinctly after the apex impulse, about 1/15 of a second after the apex impulse or the first sound at the apex. It is produced at the point of constriction of the descending limb of the thoracic aorta and is not produced until the pulse wave originating at the left ventricle reaches the point of narrowing. By the use of the sphygmograph for accurate determination of time relationships or by a combination of auscultation and palpation it is possible for the clinician to make the essential observations. Murmurs may also be heard over the prominent collateral arteries in the thorax and especially so if more than light pressure is exerted with the chest piece over them.

The author has recently studied a patient with proved atresia of the aorta immediately proximal to the renal arteries where the location of the lesion was accurately determined through use of the methods described. The systolic murmur heard over the lumbar spine was localized by the use of the sphygmograph

and it was clearly shown that the murmur originated at a point some distance from the heart by comparison with the first sound at the apex. In this case the collateral arteries developed in the pelvis were sufficiently prominent to permit palpation of their amplified pulsations.

### CONCLUSIONS

1. Four common cardiovascular lesions have been discussed from the standpoint of differential diagnosis.
2. A knowledge of the origin and means of propagation of murmurs is an important aid in the differentiation of these lesions.
3. Murmurs and thrills produced by turbulence in the blood travel on the pulse wave and not as sound from their point of origin. They may travel for short distances backward from the point of origin, i.e., from the aortic valve to the apex of the heart in aortic stenosis.

### BIBLIOGRAPHY

1. Hamilton, Wm. F.: Personal communication.
2. Levine, S. A.: Algunas observaciones referentes a los soplos cardiacos y a su modo de transmision, Arch. Inst. cardiol. México, 14:150-158 (Jan. 31) 1945.
3. Kerr, Wm. J.: Stethoscope and Sphygmograph, Medical Physics, Chicago Year Book Publishers, 1944; Sphygmograph, Sobretiro de Arch. Inst. cardiol. México, 16:58-73 (Feb.) 1946.

### The Contagiousness of Coccidioidomycosis

Coccidioidomycosis (valley fever, San Joaquin Valley fever) an infectious fungus disease has been universally regarded as noncontagious. Since no direct man-to-man or man-to-animal spread was known, isolation precautions have not been recommended. The disease is endemic in parts of Texas, Arizona, and New Mexico as well as in the San Joaquin Valley of California. It may be a benign self-limiting disease of the lung or a progressive chronic and malignant process which spreads from the lung to any or all organs of the body.

Using endospore-containing exudates from a sacro-iliac abscess, a psoas abscess and an emulsion of hilar lymph nodes from a human case, an experiment was performed where these exudates were instilled into the bronchi of 16 guinea pigs. The animals were killed over a period of 8 to 63 days and in every case there was found a lesion localized to the lung. Microscopic examination of these lesions revealed typical granulomata containing the sporangium stage of the fungus (*Coccidioides immitis*).

Many soldiers who trained in the areas where coccidioidomycosis is endemic have returned home carrying the fungus in their bodies. Spread of the disease from them to others appears to be possible from the results of these experiments and all active cases should be considered as contagious until proved otherwise.

—S. R. Rosenthal and J. B. Routien in  
*Science*, 104:479 (Nov. 22) 1946.

# Peripheral Vascular Sclerosis\*

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*The gloomy outlook in progressive occlusive arterial disease has been improving in the past decade. The authors discuss some of the points in diagnosis and management of these diseases.*

The problem of arteriosclerotic peripheral vascular disease is one of ever-increasing importance because of the advancing average age of the population. It has been estimated that there are now more than nine million people in the United States over 65 years of age, a majority of whom are likely to suffer from some measure of arteriosclerosis.<sup>1</sup> The addition to this number of the not uncommon younger individual manifesting arteriosclerotic disease presents a problem of importance not only to the individual but to society as a whole. Until recently, the belief that arteriosclerosis was an inevitable result of the process of senescence coupled with the lack of co-ordinated knowledge concerning the etiology and pathologic physiology of this disease resulted in an unnecessarily pessimistic attitude toward this problem. In fact, therapy was largely limited to the treatment of gangrene, a complication representing the end-stage of the sclerosing process. Treatment of the early complications of peripheral ischemia was frequently neglected and little effort was made to minimize the disability resulting from even the late complications. It is our purpose to show that the treatment of arteriosclerosis should not be limited to watchful but hopeless expectancy since often something may be accomplished therapeutically not only to alleviate many of the symptoms of vascular sclerosis but also to prevent or delay the progress of this disease.

## INCIDENCE

Although peripheral arteriosclerosis occurs predominantly after the fifth decade, about 30 per cent of the cases are to be found in the younger age group, and the incidence in the latter group is apparently increasing. Statistically, arteriosclerosis is most common in persons who are obese, who have hypertension, and in persons subject to severe and prolonged

emotional stress. The disease is less common in females than males despite the greater longevity of the female.<sup>2</sup> There is, in general, little to indicate that heredity or racial stock are important predisposing factors. Ophüls has reported the following data relative to the incidence of arteriosclerosis with respect to age.<sup>3</sup> It must be remembered, however, that this is not clinical, but postmortem material.

AGE	ARTERIOSCLEROTICS
20-29	3.5 %
30-39	9.25
40-49	26.0
50-59	48.0
60-69	78.0
70 and over	90.0

## ETIOLOGY

The etiology of arteriosclerosis and the factors which predispose toward its development are still in a somewhat confused state, despite vast amounts of research and clinical work. The explanation is, of course, that arteriosclerosis is not really a single disease but rather a syndrome and that not one but many factors are involved in the production of this symptom-complex. Any single theory which would explain the not uncommon absence of arteriosclerotic lesions in aged persons, the occasional presence of advanced arteriosclerotic lesions in young individuals, the irregular involvement of the arterial tree and the relationship of this involvement to particular anatomic locations, the histologically different pathology found in clinically similar cases, and the relationship between certain definite endogenous or exogenous causal factors and arteriosclerotic disease as well as the result of the experimental data on the subject must necessarily be very general and inclusive. Hueper<sup>2</sup> believes that the fundamental etiology of arteriosclerosis is interference with the oxidative metabolism and nutrition of the vascular wall. This damage produced by various causal agents and causal mechanisms result in the eventual production of focal degenerative organic lesions in the vascular system due to local anoxemia, the character and extent of the lesions being determined by both the character and duration

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of the insult in combination with both local and general conditions. He recognizes a number of conditions which may be local or general, endogenous or exogenous as a result of which spontaneous or experimental arteriosclerosis may be produced.

### CLASSIFICATION

Although Hueper's classification is of value from a didactic standpoint, it is often impossible to state in any given case just what factor is of primary importance. However, this is usually a problem of academic interest since when the damage has already been done the important thing is an estimation of the degree of damage done and the most economical and efficient mode of salvage so far as the patient is concerned. For this purpose, the following clinical classification of arteriosclerotic peripheral vascular disease was previously presented by one of us (G. deT.). This has been summarized in table form below.<sup>4</sup> (Table I.)

he has had no previous history of peripheral vascular difficulty and no causal or embolic phenomena.

The presence of occlusive peripheral vascular disease can be readily detected by means of the following clinical observations.

*Palpation of major arterial pulsations*, that is, the femoral, popliteal, dorsal pedal and posterior tibial pulses, is essential. Rarely can a diagnosis be made of obliterative vascular disease unless pulsation of one or more of these vessels is diminished or absent. It is, however, not uncommon to fail to obtain a dorsal pedal pulsation at times, even in normal individuals. Such a finding is of no significance in the absence of other evidence of disease. The use of the oscillometer has been advocated to detect weak pulsations but its use is restricted to vascular clinics and is helpful in detecting differences between symmetrical areas. Arteriolar disease may be present with intact pulsation.

The *skin temperature*, as recorded by the exam-

TABLE I  
*Clinical Groups of Arteriosclerotic Peripheral Vascular Disease*

GROUP	LOSS OF PULSES	TEMP. CHANGES	COLOR CHANGE	EDEMA	CLAUDICATION	REST PAIN	TROPIC CHANGES			ULCERATION	GANGRENE
							OSTEOPOROSIS	MUSCLE DYSTROPHY	SKIN CHANGES		
I	— or partial	slight	—	—	2-6, blocks	—	—	—	—	—	—
II	partial or complete	*	*	*	0-2 blocks	*	moderate — or absent —	slight	slight	*	—
III	*	*	*	*	Severe pain even on rest (causalgic)	*	**	**	**	*	*
IV	*	*	*		some	some	*	*	*	*	*

\* = present.

\*\* = advanced.

— = absent.

### DIAGNOSIS

A diagnosis of "arteriosclerotic peripheral vascular disease" can be made, first, by demonstration of the presence of occlusive arterial disease and, second, by the exclusion of the presence of other more clearly circumscribed clinical vascular diseases as well as certain other nonvascular conditions which might simulate vascular symptoms. However, a presumptive diagnosis of arteriosclerosis can be made with a high degree of certainty merely from the fact that a patient is over 55 years of age and by eliciting the information that

iner's hand, will amply record relatively minute temperature differences between the proximal and distal portions of the extremity. A temperature difference in the two extremities is of obvious significance. To detect any temperature gradient, this examination must not be carried out until the extremities have been exposed in a room of cool or moderate temperature for a sufficiently long period of time to discount the insulating effect of clothing or misleading results due to a warm environment. Minute temperature differences can be more accurately appraised by means

of a skin thermometer or electrical thermocouple, but this is probably an unnecessary refinement of technic even for estimation of temperature elevations of the extremities following sympathetic blocks, general or spinal anesthesia.

The *observation of skin color* is informative since it is dependent upon the vascular condition of the skin and probably represents with a fair degree of accuracy the circulatory status of the underlying structures. Skin color in occlusive disease is characterized by cyanosis of varying degrees on dependency and pallor on elevation. If on elevation of the feet for two minutes excessive blanching occurs and if on lowering the feet return of color is delayed beyond 15 seconds, some degree of arterial insufficiency exists. Use of the reactive hyperemia test in which the extremity is drained of blood and a constriction applied for several minutes before release will also demonstrate inadequacy of the circulation by slow or incomplete extension of a hyperemic blush down the leg in cases of arterial insufficiency.

The *presence or absence of trophic changes* should be looked for and will be apparent to the critical eye if circulatory embarrassment is severe and of long duration. These changes may be manifested by impairment or deformity of nail growth, absence of hair over the phalanges, or the presence of thin, smooth, shiny atrophic skin. Further observation may disclose atrophy of the subcutaneous tissues or muscles or edema of these tissues. The relationship of actual ulceration or gangrene to the pathologic picture will be clear, although the presence of a localized osteomyelitis secondary to this may momentarily confuse the primary diagnosis.

*Intermittent claudication*, the appearance of muscle fatigue followed by cramps and pain upon slight exercise, is a characteristic symptom arising from tissue anoxia which is found relatively early in the course of vascular sclerosis. The degree of arterial insufficiency is roughly proportional to the amount of activity required to produce this pain. Hence, by noting the time of onset of claudication in a patient walking at a rate of 120 steps a minute, it becomes possible to detect progression of his arterial insufficiency on subsequent examinations; or by noting the claudication time following sympathetic block one is able to measure temporary functional improvement due to the relaxation of associated vasomotor spasm.<sup>5</sup>

#### DIFFERENTIAL DIAGNOSIS

Having demonstrated by means of these tests the presence of arterial insufficiency, it remains but to rule out the presence of other peripheral vascular diseases

such as Buerger's disease, Raynaud's disease, scleroderma, and venous insufficiency to make a diagnosis of arteriosclerosis. Although from a surgical standpoint the differentiation of Buerger's disease and Raynaud's disease from arteriosclerosis is mainly of academic interest since all the members of this group respond rather favorably to sympathectomy, the diagnosis is important with regard to prognosis and to a lesser extent with respect to medical therapy.

*Buerger's disease* occurs almost entirely in males in the third to fifth decade. A history of recurrent attacks of migratory, segmental, inflammation of both arteries and veins is almost always obtainable and is characteristic. The upper as well as the lower extremity is involved in the course of the progressive vascular obliteration. Absence of a radial pulse is always suspicious of Buerger's disease. The blood count is normal or high, the cholesterol is low. Calcification in the vessels of the thigh is absent in contradistinction to arteriosclerosis.

*Raynaud's disease*, in contrast to arteriosclerosis, is most commonly found among young women. The upper extremity rather than the lower is most frequently the source of complaint. In these cases there is a definite history of exaggerated vasomotor response to cold stimuli resulting first in pallor to be followed by cyanosis and finally redness before there is a return to the prespasm state. Although Raynaud's disease may be complicated by the presence of small areas of ulceration or gangrene of the finger tips, obliteration of the major arteries does not occur and consequently it rarely if ever becomes necessary to resort to amputation in this condition.

*Scleroderma*, which in its earlier stages somewhat resembles Raynaud's disease, like it, occurs almost exclusively in young women. In its later stages the skin becomes tense and unyielding, the subcutaneous tissues atrophy and trophic changes and ulcerations may appear though usually in the upper extremity. X-rays of the extremity may show bony decalcification in the presence of calcification of small areas of subcutaneous tissue. These marked skin changes combined with the not infrequent signs of visceral involvement associated with this condition in the absence of organic vascular occlusion of the major peripheral arteries simplifies the differentiation from arteriosclerosis.

*Venous insufficiency* may be readily detected by the presence of venous congestion. Improvement rather than increased discomfort on exercise, warmth of the extremity, absence of ischemic necrosis or trophic changes in the digits though phlebotic edema or ulcerations may be present on the ankles, and finally

evidence of good peripheral arterial pulsations will complete the pictures of venous rather than arterial difficulty.

Confusion of arteriosclerosis with nonvascular diseases such as primary osteomyelitis, gout, metatarsalgia, arthritis and peripheral neuritis can be banished by a careful history combined with careful physical examination of the extremity. Osteoarthritis of the lumbar spine and arteriosclerosis of the spinal cord often accompany or mask symptoms of peripheral vascular sclerosis.

To illustrate the problems commonly met with in arteriosclerosis, the following case histories, examples of four distinct stages in the development and progression of peripheral vascular disease, are presented.

**GROUP I.** K. B., a woman, aged 69, entered the Illinois Research and Educational Hospital Dispensary on July 17, 1941 complaining of pain on walking one or two blocks. Examination revealed absence of trophic changes or ulcerations, bilateral absence of posterior tibial and dorsal pedal pulsations, pallor on elevation and cyanosis on dependency of both extremities, diminished skin temperature of both feet, and diminished histamine flares below the upper one-third of the leg bilaterally. Further examinations revealed no evidence of diabetes but signs of generalized arteriosclerosis. This patient was instructed in the care of the feet, placed upon small doses of luminal and theobromine with sodium salicylate gr. x q.i.d., and was given 40 hours of Pavex therapy over a period of weeks. She was then placed on intermittent venous compression exercises at home. After several months the patient stated that she was able to walk further without claudication and clinically the feet felt warmer and faint pulsations were detected in several of the peripheral arteries.

**GROUP II.** A. S., a man, aged 52, entered the Illinois Research and Educational Hospital on May 10, 1945 complaining of numbness and coldness of the feet, particularly on the right, of two years' duration. Examination demonstrated absence of pulses from the right extremity except for the femoral artery and on the left only absence of the posterior tibial pulsation. Typical color changes and coldness of the feet indicative of arterial insufficiency were present bilaterally, and claudication occurred on walking less than one block. No ulcerations nor obvious trophic changes were evident. A right lumbar sympathetic block with 1 per cent novocaine resulted in elevation of the temperature of this extremity and prolonged claudication time. Hence, on June 5, 1945, a right lumbar sympathectomy was performed. When last seen seven months after surgery, the patient had experienced relief of symptoms referable to his right leg and the right leg and foot were warm and dry.

**GROUP III.** C. A., a man, aged 58, entered the Illinois Research and Educational Hospital on August 17, 1945 complaining of pain and coldness of the left foot which had been getting progressively worse for the preceding year. Six months prior to admission he developed a nonhealing

ulcer of the left great toe. Examination revealed absence of all pulsations below the femoral artery on the left and absence of the left posterior tibial pulsation. Color changes, diminished skin temperature, absent oscillometric readings, and reduced histamine flares, in the presence of trophic changes completed the picture of arterial insufficiency. Temperature readings on the left leg improved markedly following sympathetic block and so on August 21, 1945 a left lumbar sympathectomy was performed. Postoperatively over a period of several months the ulcer of the big toe healed, the patient experienced a relief from pain and gained weight and the skin of the left extremity remained warm and dry.

**GROUP IV.** S. V., a male, age 66, entered the Illinois Research and Educational Vascular Dispensary on May 4, 1944 with the complaint of numbness and coldness of the left foot and swelling of this foot. He stated that he had pain in this foot even at rest, though this could be partially alleviated by placing it in a dependent position. Physical examination disclosed absent pulses below the knee, coldness of both feet, and typical color changes of arterial insufficiency bilaterally. A left lumbar sympathetic block elevated skin temperature from 26° to 29.5° C. On May 16, 1944 a left lumbar sympathectomy was done. Postoperatively the left leg became warm and dry and he had relief from his pain. However, on October 2, 1945 this patient returned to the clinic, at which time the right leg, previously the better leg, now showed an area of frank gangrene on the dorsum of the foot, whereas the left leg still remained warm and dry and the skin was in good condition. On October 16, 1945 it became necessary to do a right supracondylar amputation. The specimen removed showed occlusion of the major vessels by arteriosclerotic changes.

#### MEDICAL MEASURES IN PERIPHERAL ARTERIOSCLEROSIS

It is evident that the treatment of peripheral arteriosclerosis is both medical and surgical and in addition it should be prophylactic as well as therapeutic. The medical treatment of arteriosclerosis is definitely limited by certain considerations. Although there is an element of vasospasm present in arteriosclerosis, it is an organic disease and once a vessel has become occluded, no form of medical therapy will cause it to reopen. However, though it is a generalized disease, its distribution is patchy and its course is only slowly progressive. Under these circumstances, therapy is best directed toward measures designed to prevent injury or infection to tissues whose vitality has been impaired by deficient blood supply, the production of vasodilatation, the encouragement of collateral circulation, and the symptomatic relief of pain.

Care of the feet in persons suffering from peripheral vascular disease is so important that we have summarized this care in a sheet of instructions, which is given to each patient.<sup>6</sup>

## Illinois Research and Educational Hospital Vascular Clinic

### GENERAL DIRECTIONS FOR HOME CARE OF THE FEET

1. Wash feet each night with neutral (face) soap and warm water.
2. Dry feet with a clean soft rag *without* rubbing the skin.
3. Apply rubbing alcohol (70%) and allow the feet to dry thoroughly. Then apply a liberal amount of vaseline or toilet lanolin and gently massage the skin of the feet.
4. *Always* keep your feet *warm*. Use woolen socks or wool-lined shoes in the winter and white cotton socks in warm weather. Use a clean pair of socks each day.
5. Use loose-fitting bed-socks instead of hot-water bottles, electric heaters or any other form of mechanical heating device.
6. Wear properly fitting shoes and be particularly careful that they are not too tight. Use shoes made of soft leather and without box toes.
7. Cut your toe-nails only in very good light and only after your feet have been cleansed thoroughly. Cut the toe-nails straight across.
8. Do not cut your corns or callouses.
9. Do not wear circular garters.
10. Do not sit with your legs crossed.
11. Do not use strong antiseptic drugs on your feet. Particularly never use tincture of iodine, lysol, cresol or carbolic acid.
12. Go to your *doctor* at the first signs of a blister, infection of the toes, in-growing toe-nail or trouble with bunions, corns or callouses.
13. Drink at least four quarts of water each day.
14. Eat plenty of green vegetables and fruit in an otherwise well-balanced, liberal diet, *unless* you have been ordered to follow some *special diet*.
15. Do not use tobacco in any form.
16. Have some member of your family examine your feet at least once each week.
17. Carry out the exercises prescribed by your *doctor* exactly as you were taught to do them in the Clinic. Do them regularly and faithfully.

*Dietary therapy* is of limited importance in arteriosclerosis. Possibly a low-fat diet is desirable if diabetes is a complicating factor. In patients whose blood cholesterol is above 250 milligrams per 100 cc. of blood, diet, thyroid or iodides can be used to lower this figure. Care should be taken that obesity is not permitted to occur or persist, since this factor will add to the burden of the already overtaxed extremities and is secondarily of importance by way of its relationship to the production of hypertension and hence vascular strain. Coffee, tea and alcohol need not be eliminated from the diet since these substances possess some vasodilatory effect which may be of some benefit. Supplementary vitamin therapy has not been shown to be of any definite value although if the severity of the pain in a given case leads one to believe that a peripheral neuritis is coexistent, the addi-

tion of vitamin B-complex to the diet would seem to be indicated.<sup>7</sup>

Mention should be made of *vasodilating drugs*, some of which may produce an appreciable beneficial effect. Theobromine, particularly if combined with sodium salicylate, will effect both subjective and objective improvement in many mild cases of arterial insufficiency.<sup>8</sup> The use of nitrites, particularly the longer acting types, will aid in removal of the vasospastic elements associated with arteriosclerotic disease.<sup>2</sup> Atropine and papaverine, which have an antispasmodic effect are better reserved for use in the treatment of acute vascular occlusion.<sup>9</sup> Obviously, the beneficial effect of these medications is predicated on continued use, which in certain instances may pose the problem of tolerance and addiction. The use of anticoagulant therapy with the idea of reducing the incidence of vascular thrombotic occlusion which is associated with arteriosclerosis has been suggested, but the prolonged administration of such drugs carries with it a probably unwarranted risk, even if the patient is under relatively close observation.

*Intermittent venous hyperemia* has been shown to be of definite value not only in the temporary relief of pain due to ischemia, but also in producing maximal dilatation of the collateral vascular channels and peripheral vasospasm thus maintaining adequate circulation in cases with severe arterial insufficiency.<sup>10</sup> However, there are certain contraindications to the use of this procedure, namely: the presence of acute infection, the presence of spreading gangrene, and the presence of associated venous stasis. If venous return is obstructed by a pressure of 60–80 mm. of mercury for a period of 45–60 seconds, the accumulation of tissue metabolites and the filling and stretching of the minute vessels of the vascular tree will produce a reactive hyperemia in the extremity which is independent of nervous impulses. This hyperemia may be repeated frequently, about twice as long a period of constriction as release being required to permit repayment of the oxygen debt produced by the period of obstruction and to allow the emptying of the oxygen deficient blood from the extremity. The latter may be facilitated by elevation of the extremity on a pillow during treatment. Favorable response is also facilitated by the concomitant utilization of antispasmodic drugs or the use of heat up to 100° F. on the abdomen to induce a reflex dilatation of the peripheral vascular tree. The use of heat directly to the extremity is inadvisable since by so doing the rate of local oxygen consumption is increased and pain may be accentuated. The Buerger-Allen postural exercises and the oscillating bed are modes of therapy

which rely upon the same principles utilized in rhythmic constriction. The Pavaex boot has a similar purpose, though the apparatus is too large and expensive for prolonged use in the home and can be readily supplemented by the small, portable machine producing venous stasis. Not infrequently, by these measures the patient can be afforded temporary relief from pain and occasionally impending gangrene can be averted.

### SURGICAL MEASURES IN PERIPHERAL ARTERIOSCLEROSIS

Recently it has become evident that surgery has more to offer the arteriosclerotic patient than the removal of painful or gangrenous parts.<sup>4</sup> In the case of arteriosclerotic disease of the lower extremity, a lumbar sympathetic ganglionectomy may be indicated for the following reasons. Such an operation will not only remove any vasomotor spasm, which is so frequently associated with arteriosclerosis in some degree, but will allow persistent vasomotor paralysis of the peripheral vascular bed thus doing away with the necessity for less effective and prolonged antispasmodic medication. It is worth noting that when the sympathectomized extremity is in the dependent position, an uncompensated stretching of the vessels of the lower extremity is produced which will aid in increasing local blood supply. In the limb with sympathetics intact, vasoconstriction occurs on standing. Sympathectomy will also eliminate the unfavorable fluctuations in vasomotor tonus which would normally result from response to cold or emotional stimuli, responses which are detrimental in an extremity whose blood supply is already precarious. A dry limb is obtained and this will tend to reduce the hazard of maceration of the skin of the feet and the dangers of epidermophytosis which often provide the starting point for severe local or spreading infections. Clinically, improvement may be manifested following surgery by the presence of a warmer dryer extremity, prolongation of the claudication time if the patient is ambulatory or relief of rest pain if the patient is a more advanced case. In these Group III cases, sympathectomy may make the difference between successful resistance to local infection and the development eventually of a painful ulcer which only months of bed rest will heal if healing occurs at all. Even in Group IV by means of sympathectomy it may be possible to so increase circulation to an extremity that local removal of a gangrenous digit may be successfully accomplished instead of a lower leg amputation or a lower leg amputation may be accomplished suc-

cessfully under circumstances where otherwise a supracondylar amputation would be required.

In view of the possibility that either systemic or local conditions may contraindicate or modify surgery in a given patient, it is always advisable to evaluate these factors as accurately as possible. General operability will be influenced by the presence of severe cardiac, renal, or pulmonary involvement though relatively few patients need be refused surgery unless fatal termination from these conditions is but a matter of months since the mortality rate of sympathectomy is below 0.5 per cent (in a personal series of over 500 sympathectomies there has been no operative mortality) and the incidence of complications resulting from surgery minimal. Retinoscopy and electrocardiography will aid in estimating the patient's vascular status. Roentgenograms of the extremities may give evidence of calcification of the major vessels, osteoporosis, or in infected cases, the presence of an unsuspected secondary osteomyelitis.

The information obtained by simple special diagnostic methods is of importance and will be mentioned briefly. By means of the histamine flare test, in which 0.1 cc. of a 1:1,000 solution of histamine phosphate is injected intradermally, one can determine the adequacy of local circulation. If a notable wheal accompanied by a zone of erythema and local dilatation of the capillaries fails to appear at the site of injection within five minutes, there is evidence of local impairment of circulation to such a degree that healing of an amputation at this level would be doubtful. The use of these flares at varying levels on the extremity will allow determination of the point at which vascular supply is adequate to insure healing.

Lumbar sympathetic block with 1 per cent novocaine, a procedure described elsewhere, is not difficult to perform and is safe if the proper precautions are taken. By interruption of the sympathetic nerve supply to the extremity one is able to gain insight into the degree of improvement in peripheral circulation which might be anticipated from sympathectomy. Often, however, failure to improve local circulation by this method does not rule out the possibility of gradual improvement resulting from surgical removal of the sympathetics. On the contrary, the favorable response obtained by sympathetic block generally but not always augurs for a marked clinical improvement of substantial duration.<sup>11</sup>

The technic of lumbar sympathectomy employed by us has been described elsewhere.<sup>12</sup> Routinely we advocate a muscle-splitting extraperitoneal approach under spinal anesthesia. Removal of the second and third lumbar sympathetic ganglia on one side can

usually be accomplished in about 30 minutes. If removal of the sympathetic chains bilaterally is desired, the opposite side can be removed a week later, following which the patient can leave the hospital in a week to ten days. We have yet to experience a mortality as a result of several hundred sympathectomies done for various peripheral vascular diseases and morbidity has been surprisingly low considering the age of the patients, a fact for which the avoidance of general anesthesia and the use of early ambulation is probably responsible.

### SUMMARY

1. Arteriosclerosis is the commonest cause of peripheral vascular disease and its importance is increasing, due to aging of the population.

2. A multiplicity of factors appear to be involved in the genesis of arteriosclerosis.

3. Simple diagnostic tests for peripheral arterial insufficiency are briefly mentioned.

4. The differential diagnosis of peripheral arterial disease is discussed.

5. Case reports of representative cases of arteriosclerotic peripheral vascular disease are presented.

6. Medical and surgical measures of value in the treatment of peripheral arteriosclerotic vascular disease are described.

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### Expanding Medical Research

A large-scale, nationwide, peacetime program of support for scientific research in medical and related fields, guided by more than 250 leading scientists in 21 principal areas of medical research, is now a functioning reality. The program, based on U. S. Public Health Service Research Grants financed by public funds, supports research—conducted without governmental control—by independent scientists. The purpose of these grants is to stimulate research in medical and allied fields by making available funds for such research and by actively encouraging scientific investigation of specific problems on which scientists agree that urgently needed information is lacking. Accompanying this purpose is complete acceptance of a basic tenet of the philosophy upon which the scientific method rests: The integrity and independence of the research worker and his freedom from control, direction, regimentation, and outside interference.

### BIBLIOGRAPHY

1. Stieglitz, E. J.: Report of a Survey of Active Studies on Gerontology, Unit of Gerontology, Division of Chemistry, Nat. Inst. Health, U. S. Public Health Service, 1942.
2. Hueper, W. C.: Arteriosclerosis, a general review, *Arch. of Path.*, 38:162–181, 245–285, 350–364, 1944; 39: 51–65, 117–131, 187–216, 1945.
3. Ophüls, W.: The Pathogenesis of Arteriosclerosis. In Cowdry, E. V.: *Arteriosclerosis*, New York, Macmillan, 1933.
4. deTakats, G., E. F. Fowler, and P. Jordan: Sympathectomy in peripheral vascular sclerosis, *J. A. M. A.*, 131:495–500, 1946.
5. Barker, N. W., G. E. Brown, and G. M. Roth: Effect of pancreatic tissue extracts on muscle pain of ischemic origin, *Tr. Am. Therap. Soc.*, 33:115–119, 1933.
6. deTakats, G., W. C. Beck, and E. Roth: The neuro-circulatory clinic. A summary of its activities. I. Peripheral vascular disease, *Ann. Int. Med.*, 13:957, 1939.
7. Allen, E. V., N. W. Barker, and E. H. Hines: *Peripheral Vascular Diseases*, Philadelphia, Saunders, 1946.
8. Scupham, G. W.: Effect of theobromine on peripheral vascular disease, *Arch. Int. Med.*, 54:75, 1930.
9. deTakats, G.: The use of papaverine in acute arterial occlusions, *J. A. M. A.*, 106:1002, 1936.
10. deTakats, G., F. K. Hick, and J. S. Coulter: Intermittent venous hyperemia in the treatment of peripheral vascular disease, *J. A. M. A.*, 108:1951–1959, 1937.
11. Grimson, K. S.: Sympathectomy and the circulation— anatomic and physiologic considerations and early and late limitations, *Surgery*, 19:277–299, 1946.
12. deTakats, G.: The technique of lumbar sympathectomy, *S. Clin. North America*, 26:56, 1946.

The U. S. Public Health Service Research Grants, in operation as a medical research program of scientists and by scientists, may have early and profound effects upon the course of medical history and the national health.

The program, both in principle and as administered, has been welcomed and approved wholeheartedly by leaders in medical research. A total of 264 research projects, supported by \$3,900,000 granted from the inception of the program late in 1945 up to 15 October 1946, already have been undertaken in 77 universities, hospitals, and other public and private institutions in 26 states. Although the program is less than a year old and has been little publicized, interest is rapidly widening, and new applications already are being received at a rate greater than 800 per year.

—C. H. Van Slyke, *Science*, 104:559  
(Dec. 13) 1946.

# Management of Vivax Malaria in the Veteran\*

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*For some time to come doctors will be seeing cases of relapsing or delayed primary attacks of malaria. Some of these will be encountered in nonmalarial areas for the first time. The usual as well as the unusual features of this disease and its management are well described in this article by one who has had a wide experience in this field as Chief of the Tropical Disease Section of the Medical Service of the Moore General Hospital. This hospital was designated as a center for tropical diseases.*

As a result of military operations in various tropical areas approximately a half a million cases of malaria developed in our troops. Fortunately suppressive measures with atabrine were on the whole effective in controlling these infections and malaria did not interfere with the successful execution of the war. Falciparum infections produced little morbidity and practically no mortality. Further it was found that the proper use of atabrine resulted in definitive cure of these infections. The major clinical problem with regard to malaria was the result of repeated relapses due to vivax infections particularly those of Pacific origin. However, experience has now shown that with the elapse of time the number of patients subject to relapse has progressively declined so that within several years the problem of relapse from war-acquired vivax malaria will be insignificant.

The great interest in malaria during the war and the extensive research program in the search for new drugs produced significant results. Re-evaluation of existing antimalarial drugs furnished valuable information on the clinical shortcomings, toxicity, pharmacology and relative efficiency of quinine and atabrine and resulted in the most effective use of atabrine. New drugs were developed which proved superior to quinine and atabrine for suppressive and therapeutic purposes. Finally a schedule of treatment with *pamaquine* (plasmochin) was found which proved curative in a high percentage of vivax infections.

The purpose of this communication is to present briefly the practical application of the above studies in the management of malaria in the veteran and in general practice.

## CLINICAL ASPECTS OF VIVAX MALARIA

The clinical diagnosis of vivax malaria in this country is not difficult as a rule. The patient, in many instances, can suggest the correct diagnosis at the onset of an attack, and this can usually be confirmed by the demonstration of malarial parasites in one or more examinations of blood smears. There is a history of residence in an endemic area and, except for the first attack, there have been previous similar attacks. The symptoms of a "paroxysm" (acute attack) as a rule are quite characteristic, consisting of chilliness followed by a chill of varying severity and high fever of short duration followed by sweating, headache, backache, generalized aching and malaise, weakness, abdominal pain and tenderness and frequently nausea and vomiting. Vague muscular and joint pains, malaise, headache, backache and slight fever may precede the acute attack by several days.

Without treatment, paroxysms recur daily or every other day for a varying period. In a small number of patients spontaneous recovery from the acute attack takes place after one or more days, while in the majority of untreated patients the disease continues its activity for an extended period. With proper treatment there is prompt control of fever and other symptoms, and usually recovery from the acute attack is complete within a week. Complications or sequelae are rare, but one or more relapses follow in a majority of cases. Relapse rates for infections of Pacific and Mediterranean origin are approximately 80 per cent and 30 per cent respectively.

The clinical manifestations of the paroxysm described above are usually sufficiently characteristic to make the diagnosis of vivax malaria an easy one to establish in most cases. However, certain uncommon manifestations of this infection may be encountered which are of clinical importance. Appreciation of their relation to vivax malaria may facilitate early correct diagnosis and avoid unwarranted types of non-specific therapy.

### A. "DELAYED PRIMARY" ATTACKS SIMULATING FEVERS OF UNKNOWN ORIGIN

Military or civilian personnel who have been on duty in endemic areas and have taken quinacrine (ata-

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brine) regularly in sufficient amounts for effective suppression will give no history of malaria while overseas. Sooner or later after they have returned to the United States they will discontinue taking suppressive medication. Those who have been infected with *P. vivax* will exhibit clinical signs and symptoms of active malaria within several weeks or months after stopping quinacrine. The onset of the disease in this group, as well as in primary attacks when no antimalarial had been taken, frequently does not conform to that usually associated with malaria by the general practitioner. The disease may begin insidiously with malaise and headache. The temperature, which is elevated slightly at the onset, rises gradually, or abruptly within a few days to 103° or 104° F. and the pattern of the temperature may be completely irregular or of a septic remittent type. Severe shaking chills, which are so characteristic of relapses, may be absent during the first few days of the delayed primary attack despite high fever. Further, and often confusing to the physician, is the fact that one or two routine smears made early may be negative for malaria parasites. I have seen patients with delayed primary vivax malaria who, despite high fever and daily chills, had negative thick smears (less than 1 parasite in 72 squares, 0.1 cu. mm.) and were examined twice daily for from two to five consecutive days before parasites could be demonstrated. When parasites do appear they may be present in relatively small numbers, in contrast to a relapse, in which the smears are usually positive on the first examination and the parasite count is relatively much higher.

The quandary of the physician faced with a patient who has been sick for several days with rising fever, vague complaints and little in the way of physical findings is apparent. The white blood cell count is usually low, and if the spleen is palpable one may think of typhoid or some other bacterial blood stream infection. The temptation to prescribe sulfonamides or penicillin is great, especially if the first few blood smears are negative for parasites, and I have seen patients with this type of onset who received large amounts of penicillin without benefit.

Unless laboratory facilities are not available, unexplained fever in the returned serviceman should not be treated until a definite diagnosis has been established. Thick smears should be examined twice daily by a trained technician and continued for at least a week. In the meantime, other diagnostic studies can be carried out without compromising the patient's chances of recovery by waiting or withholding therapy. If malaria parasites are demonstrated, the disease has been correctly documented and this is impor-

tant as a baseline for future recurrences of a similar nature. It must also be remembered that in a few individuals the delayed primary attack may occur as long as a year after suppressive medication has been discontinued. Nevertheless it is helpful in the management of cases of fever of unknown origin as described to know whether the patient has been in endemic malaria areas, when he stopped suppressive medication and whether he has had similar episodes previously controlled with antimalarial medication.

#### B. SIMULATED PRIMARY ABDOMINAL CONDITIONS

1. **Acute Episodes.** Attacks of vivax malaria are frequently accompanied by gastro-intestinal symptoms and signs of varying severity. Nausea, vomiting and abdominal pain and tenderness are common, usually follow the paroxysm and are rarely of such intensity as to confuse the diagnosis of malaria. In a small number of patients, however, the abdominal symptoms and signs may precede the paroxysm by a day or two and be of such severity as to suggest a primary acute abdominal condition, particularly acute appendicitis, intestinal obstruction or acute cholecystitis. Unless one is aware of this possibility, needless surgery may be performed. In contrast to the usual findings in acute appendicitis the abdominal pain in malaria is more diffuse, tenderness is present in both lower quadrants, muscular rigidity is absent and rectal examination is not localizing.

In a small number of patients an attack of malaria may be preceded by several days or ushered in with a period of brisk watery diarrhea. If fever and vomiting occur before the chill, one may suspect acute gastro-enteritis. The smears are almost always positive and within a short time the typical chill, high fever and other symptoms will suggest the correct diagnosis. In many of these cases the symptoms accompany each relapse and a good history is extremely helpful.

2. **Signs and Symptoms of a Chronic Nature.** Occasionally protracted low-grade malarial activity in some individuals with good immunity may be manifested by slight to moderate anemia, slight icterus and enlargement of the liver and/or spleen. Inadequate treatment of frequently occurring mild attacks may also produce the same findings. Either there is no fever or, if present, it is low grade. Parasites are almost always present in the circulating blood, but their density may be very low. In such a combination of findings one may suspect some intrinsic disease of the liver, gallbladder or biliary system or some hematologic disorder rather than malaria. In several such cases with a red blood count as low as 2.2 million per



cubic millimeter careful study of blood smears proved the underlying condition to be vivax infection. Specific therapy with antimalarial drugs produces a reticulocyte response, recession of the liver, disappearance of signs and symptoms and recovery from the anemia without iron or other drugs.

If the possibility is borne in mind that gastro-intestinal symptoms and signs of varying intensity or chronicity may be related to underlying infection with *P. vivax* in some cases the correct diagnosis may be established and needless surgery avoided. It is not suggested that all acute or chronic gastro-intestinal conditions occurring in patients who have had malaria are related to that disease. In fact, a moderate number of patients with a history of prior malaria suffering currently from chills, fever, abdominal or other signs and symptoms were treated without benefit with antimalarial drugs on the assumption that the findings were due to malaria. Smears were negative and the white blood cell count elevated, which is exceptional in malaria. The conditions subsequently shown to be incorrectly diagnosed as malaria were, in their order of frequency, acute follicular tonsillitis, cellulitis, thrombophlebitis, pyelitis, pneumonia and cholecystitis.

A careful history particularly of previous similar episodes related to proved attacks of malaria, physical and laboratory examinations including careful search for malaria parasites and evaluation of all the findings possibly in conjunction with a surgeon when indicated should lead to a rational plan of management of the individual case.

#### C. CENTRAL NERVOUS SYSTEM MANIFESTATIONS

Signs or symptoms referable to the central nervous system in malaria occur most frequently in severe infections with *Plasmodium falciparum*. It is for this reason that there is a tendency to label all central nervous system manifestations occurring in malaria as "cerebral malaria," with the alarming implications and necessity for vigorous treatment which severe falciparum infections carry. The changes in the brain in falciparum infections consist of occlusion of small vessels with parasitized red cells, parasites, pigment and debris, multiple small discrete or ring-shaped hemorrhages and other pathologic alterations. No such changes in the brain in vivax infections have ever been described to our knowledge. Furthermore, falciparum infections, if adequately treated or suppressed with quinacrine, rarely relapse. However, if central nervous system symptoms and signs occur at the onset of an attack of malaria and there is any question about the history or species of parasite ob-

served or if no history can be obtained, the safest procedure to follow is the institution of vigorous parenteral antimalarial therapy until it can be decided whether or not the infection is due to *P. falciparum*.

Definite and severe symptoms and signs referable to the central nervous system at the onset of attacks of vivax malaria do occur and are worthy of note. Severe headache is common but is not alarming, and symptomatic treatment suffices. Delirium is seen in some patients and is probably an expression of hyperpyrexia in individuals sensitive to high fever. Antipyretics, sponging, parenteral fluids and ice caps to the head usually are effective in controlling this symptom. Acute psychoses may occur during treatment and represent a rare manifestation of quinacrine toxicity unrelated to malaria itself. Severe stiffness of the neck preceding or accompanied by fever and a chill at the onset of an acute attack of vivax malaria may be suggestive of meningitis which must be excluded. The spinal fluid is normal, the white blood cell count tends to be low and the blood smears contain parasites (*P. vivax*).

Convulsions at the onset of an attack of vivax malaria may be alarming but fortunately occur rarely.

The immediate diagnosis in patients with central nervous system signs and symptoms related to an attack of malaria may be difficult. Central nervous system findings in the presence of a late relapse of malaria are probably associated with vivax infection but the nervous system manifestations may be due to underlying disease of the brain such as may be found in epilepsy, following head injury or in rare cases following prior severe falciparum infections with cerebral localization. Anticonvulsant drugs should be continued in those individuals who suffer from convulsive disorders until the malaria infection has run its whole course or has otherwise been eradicated by curative treatment.

#### D. MISCELLANEOUS

1. **Respiratory Symptoms.** Upper respiratory symptoms, especially during winter months, are common in vivax malaria. Likewise, chest pain and râles are not uncommon during an attack. These findings in a patient with a chill and a high fever may suggest pneumonia. The chest x-ray is negative and smears will contain parasites, establishing the diagnosis of vivax malaria. These two diseases are not often confused, but I have seen treatment of pneumonia delayed because it was assumed that the patient had malaria, and conversely I have seen suspected pneumonia treated without effect because the patient actually had malaria. In malaria the elevation of tem-

perature is not sustained beyond a few hours after the chill, and the accompanying symptoms, negative x-ray and positive blood smears for parasites should make the diagnosis simple if both diseases are considered.

2. **Rupture of the Spleen.** This serious complication is a very rare occurrence during an attack of malaria and is mentioned only in passing. The symptoms and signs are so dramatic and the abdominal findings such that the diagnosis is usually made. Immediate surgery is indicated, following which the attack of malaria can be controlled with parenteral medication.

3. **Chills and Fever After Injuries or Operations.** It is well known that trauma, general anæsthesia or surgery may induce a relapse of vivax malaria. However, this may occur years after cessation of all malaria activity and the disease forgotten. If it is borne in mind and blood smears are examined for malaria parasites, needless worry about postoperative infection or embolization can be avoided.

4. **Chills and Fever or Jaundice After Transfusions.** Patients who are receiving repeated transfusions of fresh whole blood for an acute or chronic disease may develop jaundice, anemia or chills and fever. This may be due to activity from transfused vivax parasites rather than infectious hepatitis or hemolytic, Rh or pyrogenic reactions. The latter certainly are more common than transfusion malaria, but this possibility must not be overlooked and smears should be examined for parasites.

5. **Allergic Manifestations.** Urticaria or severe angioneurotic edema may precede or accompany acute attacks of vivax malaria. A history of such correlated episodes and examination of blood smears will frequently dispense with time consuming allergy studies in such cases.

## LABORATORY DIAGNOSIS

The diagnosis of malaria is definitively established only by the demonstration of parasites in the peripheral blood. In the case of relapses of vivax malaria in veterans parasites are usually sufficiently abundant to be found readily in ordinary thin smears. Smears which may be stained with Wright's stain in the usual manner should be examined under oil immersion. A great deal of improper emphasis has been placed on the time smears should be made in relation to the fever pattern. The correct time to make smears is when the diagnosis is suspected regardless of the period in the cycle of the parasite or the time in relation to the paroxysm. Needless time is often lost in waiting for the next paroxysm before smears are made. In fact the height of the paroxysm in a well developed

infection is the poorest time to make smears since at this time the parasites are smaller and not as well established in relation to red cells as at other times in the cycle. In the case of primary attacks the density of parasites may be so low that one or more thin smears will be negative even after careful search. In these cases, however, thick drop examinations often disclose parasites. For this reason it is a good practice to make thick and thin smears at the same time and if the latter are negative the thick smears can be examined in a laboratory or by personnel trained in the thick drop technic. If facilities for such studies are not available thin smears should be examined at 8- to 12-hour intervals for at least several days. In some cases even the thick drop may be negative and the same procedure of multiple examination for several days should be followed. Wherever possible exact species identification of the parasite should be established. In the latter connection it may be pointed out that quartan (*P. malariae*) malaria occurred very rarely in the army and that *P. falciparum* is almost never found from three to six months after the last exposure or primary attack. Reference of smears for species identification in doubtful cases to medical school, county, state, or federal laboratories is a helpful procedure.

Another misconception in regard to the laboratory diagnosis of malaria is the use of adrenalin. There is no evidence that injections of adrenalin significantly affect the parasite density in the peripheral blood. Time spent in examination of numerous smears after injections of adrenalin could be more profitably employed in thick drop examinations and in repeated examination of smears at 8- to 12-hour intervals for several days. Complement fixation, precipitin or other serologic tests are of no value in correlating a current acute illness with malaria infection. The presence or absence of malaria parasites in the blood is the crucial factor in the diagnosis.

## TREATMENT

### SYMPTOMATIC

The paroxysm of vivax malaria, i.e., the acute attack from the onset of the chill through defervescence of fever, is relatively short and rarely exceeds four hours. Nevertheless a great deal can be done to alleviate the patient's discomfort. The sensation of coldness or the actual chill which often initiates an acute attack is usually the signal for hot water bottles and numerous blankets. However, once the latter are supplied the fact that the chill may only last 20 minutes is lost sight of. As a result patients with

marked hyperpyrexia and sweating are allowed to remain excessively covered for several hours. Extra blankets and hot water bottles contribute only slight psychologic relief from the sensation of coldness. If extra covers and hot water bottles are used they should be removed as soon as the chill has ceased. Removal of pajamas and blankets permits more rapid return of body temperature to normal. In cases of hyperpyrexia acetylsalicylic acid by mouth, sponging with alcohol and fanning the nude body with several electric fans hastens recovery from fever.

In severe nausea and vomiting nothing should be given by mouth—not even ice. Patients may take large amounts of fluids in the form of ice and continue to vomit as a result. An infusion of 5 per cent glucose in normal saline solution is extremely helpful in the control of nausea and vomiting. In the absence of nausea and vomiting or following their control a liberal fluid intake is encouraged with added salt, particularly in the summer time. No limitation in diet is necessary, the patient being allowed to eat what and as much as he desires. The use of iron following an acute attack of malaria is seldom necessary for significant anemia rarely occurs in the short period of clinical activity usually associated with treated vivax malaria. Mixtures of codeine and acetylsalicylic acid may be given to control severe headache.

#### CHEMOTHERAPY

Extensive studies with antimalarial drugs have demonstrated the superiority of chloroquine over quinine, totaquine and quinacrine (atabrine). It is probable that chloroquine will soon be generally available and this drug is recommended as the antimalarial agent of choice in the routine treatment of acute attacks of vivax malaria. Chloroquine is a 4-amino quinoline compound with an extremely high order of activity against malarial parasites being effective at plasma levels as low as 5 to 10 micrograms per liter. In therapeutic amounts no significant toxicity has been ascribed to the drug. Occasionally transient pruritus of the hands and feet may occur during therapy, but this symptom usually disappears after 12 to 18 hours despite continued medication. In some patients urticaria or a transient erythematous eruption may occur but these signs are of no major toxic significance. Chloroquine does not produce any discoloration of the skin even after prolonged therapeutic or suppressive medication. Total doses of chloroquine which may be from two to four times the recommended therapeutic doses may produce in some patients blurred vision and difficulty in accommodation to near and far vision. Such doses are not advised and unnecessary for effective therapy.

**Recommended Therapy.** When the diagnosis of malaria has been confirmed by the demonstration of parasites of *P. vivax* in the peripheral blood the following schedule of therapy is advocated. The initial dose consists of 0.3 Gm. of chloroquine base. This amount of drug is contained in two tablets (each 0.25 Gm.) of aralen diphosphate, a commercial preparation (Winthrop). The same dose (0.5 Gm. aralen diphosphate) is repeated four hours later. No further specific therapy is given during the first day. On the following morning a single dose of 0.5 Gm. of aralen diphosphate is given and this is repeated on the next two consecutive mornings. Thus a full course of therapy consists of the administration of 2.5 Gm. (10 tablets, 0.25 Gm. each) of aralen diphosphate in a total of four days. The above amount of drug contains 1.5 Gm. chloroquine base.

Therapy with chloroquine as described above will result in prompt control of the signs and symptoms due to the current attack of malaria. In the majority of patients blood smears will become free of parasites within 48 hours after initiation of treatment and in practically every case no parasites will be present after 72 hours. Fever on the second or third days of treatment occurs in less than five per cent of patients treated with chloroquine. Treatment with chloroquine is not curative and approximately 80 per cent of patients with Pacific vivax infections will relapse within 120 days after treatment. However, the interval to relapse is significantly longer than after treatment with quinine or atabrine. The mean interval to relapse after treatment with chloroquine is approximately 60 days compared to 24 and 50 days after quinine and atabrine respectively. In addition short-term relapses, that is, those occurring within a month after treatment, are abolished with chloroquine since after this drug relapses rarely occur before 40 to 50 days after treatment.

In summary chloroquine is recommended as the drug of choice for the routine treatment of acute attacks of vivax malaria because of (1) ease of administration in a short course of treatment of four days, (2) absence of noteworthy toxicity, (3) prompt control of fever and other signs and symptoms of malaria, (4) prompt control of parasitemia, (5) long interval to relapse, and (6) abolition of short-term relapses after treatment. In all these respects chloroquine is superior to atabrine and quinine.

If chloroquine is not available atabrine is recommended as second choice. When the diagnosis of malaria has been confirmed by a positive blood smear a single dose of 0.4 Gm. of atabrine is given. After an elapse of from six to eight hours another dose of 0.3 Gm. is given and this is repeated after another

six or eight hours have elapsed. No further specific medication is given during the first 24 hours. On the second day 0.1 Gm. is given three times daily after meals and this is continued for six days so that a total of 2.8 Gm. have been administered during seven days. No benefit is obtained by larger doses or more prolonged therapy. Gastro-intestinal symptoms may be reduced by giving the drug with meals, sodium bicarbonate, or sweetened fluids or fruit juices. Atabrine should not be given to patients with atypical lichen planus or eczematoid dermatitis since in these cases severe exfoliative reactions may occur. Rarely, acute psychoses occur during atabrine therapy. If severe vomiting and nausea preclude the use of atabrine by mouth an initial dose of 0.4 Gm. may be given intramuscularly (0.2 Gm. in each buttock). This dose may be repeated in 12 hours if vomiting has not been controlled by intravenous fluids and withholding food and fluids by mouth. In either case the total amount of drug administered by mouth and parenterally during the first 24 hours should not exceed 1.0 Gm. Subsequent medication is as previously described, namely, 0.1 Gm. three times a day for six days, so that the full course of therapy consists of 2.8 Gm. during seven days.

Therapy with atabrine as above described will produce very satisfactory control of the symptoms and signs of the acute attack of malaria. Parasites disappear promptly from the blood although a little more slowly than with chloroquine. Fever is readily controlled although a higher percentage of patients will have fever on the second or third days of treatment compared to patients treated with chloroquine. The interval to relapse after treatment with atabrine is shorter than after chloroquine and a significant number of patients may relapse within a month after atabrine therapy. In this respect particularly atabrine is inferior to chloroquine as an antimalarial agent.

Quinine is not recommended in the treatment of vivax malaria unless chloroquine is not available and the patient is hypersensitive to atabrine with relation to the skin or central nervous system. The principal shortcoming of quinine as an antimalarial agent is the fact that after treatment with doses as high as 3.0 Gm. daily for 14 days the majority of patients who relapse do so within three to four weeks after completion of therapy. In addition quinine produces more disturbing symptoms of toxicity than either atabrine or chloroquine. Parasites persist longer in the blood during quinine therapy than with either of the above drugs and fever in the primary attack is not controlled as promptly with quinine as with atabrine or chloroquine. In other words, no benefit results from the use of quinine and in fact its continued use in a given

case will often result in repeated attacks of malaria at very short intervals.

#### SUPPRESSION

The continued administration of antimalarial drugs after termination of the acute attack by adequate therapy will prevent the development of signs or symptoms of malaria as long as suppression is continued and provided the dosage schedule is adequate and adhered to without interruption. Suppression for a period of six months does not eradicate the infection and the probability of relapse after discontinuance of drugs is the same as in unsuppressed patients. It is possible that suppression of malaria by drugs for two or three years might permit the infection to run its course completely without symptoms of malaria during the period of suppression, but such a procedure is not practical and not without danger of serious chronic or acute intoxication from the drugs.

Except under special circumstances, suppressive medication in this country is not recommended after treatment of the acute attack. If recovery from a chronic disease such as tuberculosis may be prolonged or complicated by intercurrent attacks of malaria suppressive medication can be used. Chloroquine in single weekly doses of 0.5 Gm. (aralen diphosphate) begun a week after termination of the acute attack and continued for from three to six months has been found effective in suppressing parasitemia and symptoms and signs of malaria. In personnel who must travel or remain on the job without interruption due to acute attacks of malaria suppressive medication with chloroquine may also be employed for short periods. And finally, as a pre-operative measure in patients who have had an attack of malaria within three months prior to the contemplated operation, suppression can be instituted to prevent an attack of malaria in the postoperative or convalescent period. This can be accomplished by the administration of a total of 1.5 Gm. of aralen diphosphate in one to three days prior to operation and as a result there should be freedom from malaria for at least a month after operation. Suppression with chloroquine is more satisfactory than with atabrine because with the former drug doses may be given once a week whereas atabrine suppression must be a daily matter. Prolonged atabrine ingestion produces yellowish discoloration of the skin and in some individuals may lead to the development of severe hypoplastic or aplastic anemia, or the atypical lichen planus-eczematoid dermatitis complex.

#### CURE OF VIVAX MALARIA

Treatment of the acute attack of vivax malaria with quinine, atabrine or chloroquine does not cure the

infection. Relapses occur after treatment in 80 per cent of Pacific infections and 30 per cent of Mediterranean infections. In some individuals, repeated attacks will occur during a period of two or three years.

Studies with combined quinine-plasmochin treatment of relapsing vivax malaria conducted during the war demonstrated conclusively that such treatment produced definitive cures in at least 90 per cent of cases. Unfortunately this form of treatment has certain limitations related principally to the potential toxicity of plasmochin.

There is evidence that the major serious toxic manifestation of plasmochin, namely, severe hemolytic crises, occurs more frequently in pigmented races than in white patients. Treatment as here described should therefore be given only to white patients. A further limitation of combined quinine-plasmochin treatment is the necessity for hospitalization and careful clinical observation for the 14 days of treatment in order to recognize and combat a serious reaction if it should occur. Nevertheless the treatment is valuable in many cases and has an important place in the chemotherapy of malaria.

**Combined Quinine-Plasmochin Treatment.** In order to simplify the administration of drugs, chemotherapy is begun on the morning following the onset of the current acute attack of vivax malaria which has been confirmed by positive blood smears. At 8 A.M., 4 P.M., and at midnight quinine sulfate 0.6 Gm., and 0.02 Gm. plasmochin naphthoate are given together. Both drugs are given at the same time in the doses indicated and medication is continued at eight-hour intervals for 14 consecutive days. The full course of therapy consists of 25.2 Gm. quinine sulfate and 0.84 Gm. plasmochin naphthoate. The patient should be hospitalized during therapy, blood typed on admission, and arrangements prepared to have suitable blood for transfusion available if it should be needed. There is no way at present of anticipating a serious hemolytic crisis. The patient should be seen twice daily and clinical symptoms or signs of severe anemia sought for. The hemoglobin should be determined daily. If it falls 20 per cent or more on each of two consecutive days treatment should be discontinued. Serious hemolysis did not occur in a series of over 100 white patients treated for 14 days without interruption. If severe hemolysis is discovered treatment with whole blood transfusions and fluids intravenously should be started at once and continued until the reaction has been controlled. Cyanosis as a result of methemoglobinemia may be seen but this is not an indication for discontinuance of therapy. Likewise abdominal cramps of varying severity occur frequently but these usually disappear or become less trouble-

some with further specific therapy. During the first week of treatment leukocytosis is common and in the second week leukopenia may occur but these blood changes are usually of no clinical significance.

It is not intended as a result of this discussion of the potential toxicity of plasmochin to discourage its use. There are specific indications for the combined quinine-plasmochin treatment of malaria but its limitations must be recognized. Ideally this form of treatment should be given to white patients who can be attended frequently in a hospital for two weeks. The patient should be in good physical condition. In the case of Mediterranean infections since the probability of relapse after chloroquine or atabrine is only 30 per cent it might be wise to wait until the patient has relapsed two or three times before considering combined quinine therapy. In the case of repeated relapse of Mediterranean infections or after two or three relapses from a Pacific infection the combined quinine-plasmochin course of treatment is indicated.

More recently a new plasmochin-like drug, pentaquine, has been introduced which may be less toxic than plasmochin. If this drug is available it can be given with quinine in the manner outlined. No more than a daily total of 60 mg. of base of pentaquine (80 mg. of diphosphate) should be given. Each dose of pentaquine (20 mg. base) is given with 0.6 Gm. quinine at eight-hour intervals for 14 days. The serious toxic manifestations of pentaquine are similar to plasmochin.

## SUMMARY

It is not anticipated that malaria in the veteran will be a serious problem in civilian practice. The major problem has been the one of frequent relapse particularly in vivax infections of Pacific origin. However, the number of veterans with relapses at the present time is rapidly diminishing and within another year or two most infections will have run their course.

The uncommon clinical aspects of vivax malaria are presented to facilitate early diagnosis. Malaria should not be treated unless the diagnosis is confirmed by positive blood smears. This is particularly true in the primary attack. It should also be remembered that not all acute illnesses in the veteran ushered in by chills and fever are due to malaria and vice versa malaria may simulate other acute infections.

Chloroquine is recommended as the drug of choice for treatment of acute attacks and for suppression. The indications for suppression are outlined.

Curative treatment with combined quinine and plasmochin or pentaquine is outlined and the indications for this treatment as well as its limitations are presented.

# Diagnosis and Management of Peripheral Nerve Injuries\*

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*For the physician called upon to care for the injured, this paper discusses the problems of diagnosis, repair and postoperative management for the restoration of function in cases of peripheral nerve trauma.*

The role of the physician in the treatment of peripheral nerve injuries is two-fold. His first function is to recognize the existence of a nerve injury following open or closed wounds to the neck or extremities and see that definitive treatment is administered by one who has been trained in nerve surgery, within a reasonably short time after the injury. The second function, and in many respects the most difficult, is the supervision of the postoperative course of the patient through the long months it requires for the nerve to regenerate and re-establish its normal function.

The physician's responsibility has not changed materially but there have been definite advances made in the diagnosis and management of nerve injuries. These have been made possible by laboratory experimentation and especially by experiences acquired with the abundant material provided during the war. It seems appropriate, therefore, to review the present status of our knowledge in the diagnosis and management of peripheral nerve injuries in order that they may be treated more successfully.

The subject will be divided into problems of diagnosis, nerve repair, postoperative management, pain and results.

## PROBLEMS OF DIAGNOSIS

The most common reason for not recognizing a nerve injury following an accident is the failure to think of the possibility; or the attention of the physician is directed toward a fracture, the severity of the wound, hemorrhage, shock or other associated conditions. A wound may appear trivial and may be at a distance from any one of the main nerves of the extremity, yet be associated with complete severance of one of them. This is especially true in wounds inflicted by knives or other sharp objects and was common in penetrating or perforating war wounds of the

extremities caused by shell fragments or bullets. Another fact which is not generally appreciated is that nerves can be torn or ruptured without a break in the skin, exclusive of injuries to the brachial plexus occurring in infants during delivery or in children following a sudden upward pull on the extremity by a too-helpful parent or attendant.

It should be a routine procedure to examine for nerve injuries in all patients with neck and extremity wounds. When the patient's condition does not permit, or the cessation of hemorrhage is the all-important procedure at the moment, nerve function should be tested when circumstances are favorable. Except when hemorrhage is a major factor, a wound should never be treated surgically until an examination has been made for the presence of a nerve injury.

How can this examination be made most easily? For practical purposes, it can be assumed that all peripheral nerves are mixed nerves, that is, they contain both motor and sensory fibers. There are a few exceptions, such as the musculocutaneous which supplies the biceps and brachioradialis, and the interosseus branch of the radial in the forearm. With these exceptions, testing for pain sensation with a *pin* in the constant area supplied by each of the main nerves will reveal the state of function of that particular nerve. By this method, nerve injury can be differentiated from tendon injury and a rapid evaluation be made of the specific nerve or nerves that are paralyzed.

After the sensory examination has suggested a nerve injury, the deformity of the extremity, particularly the hand or the foot, is noted since there is a characteristic deformity for each of the main nerves. This observation adds to the evidence in favor of a nerve injury (Fig. 1, 2, 3). The strength of the muscles supplied by the nerve is then determined. The extent of the muscle paralysis will permit an estimation of the level at which the nerve is injured and whether it is partially or completely severed.

When an examination has been negative for the presence of a nerve injury, it is important to make a record of this fact. If, upon examining a patient following the removal of a cast, it is found that a nerve is paralyzed and there is no record of an examination being made before, it is impossible to say whether the

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nerve was injured at the time of the original accident or was caused by pressure of the cast or bone callous. The same reasoning can be applied to wounds which have healed. Was the nerve injured when it was received or is it the result of pressure by scar tissue? Surgical treatment is required in either case. However, the prognosis is much better and recovery is much more rapid if the paralysis is due to pressure.

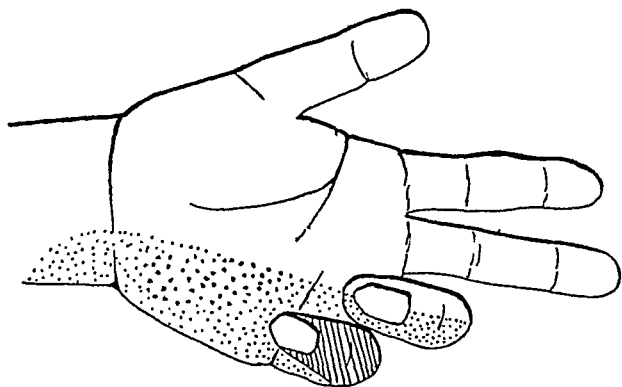


FIG. 1. Characteristic deformity for ulnar nerve paralysis. Fingers are extended. Diagonal lines—constant area of anesthesia to pin prick. Dotted area—usual pattern of sensory loss.

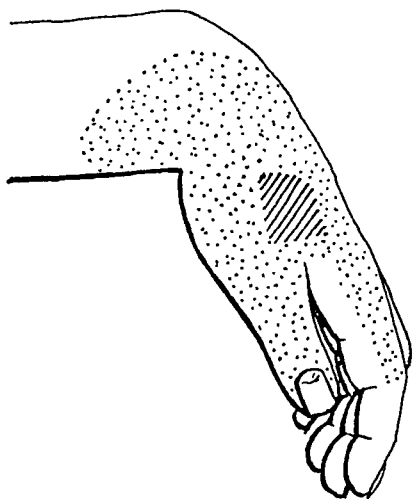


FIG. 2. Characteristic deformity for radial (musculo-spiral) nerve palsy with wrist drop. Diagonal lines—most constant area of anesthesia to pin prick. Dotted area—usual pattern of sensory loss.

The next problem which must be solved after a nerve injury has been ascertained, is the differential diagnosis between anatomic and physiologic interruption. Anatomic interruption signifies a partially or completely torn nerve, whereas physiologic interruption is the loss of the conductive power of the nerve while its physical aspect remains grossly

normal. The importance of making this decision is that in the latter instance, recovery of the nerve will take place without surgical intervention. There is no method at the present time which will help make this decision when the nerve paralysis is first discovered. Electrodiagnostic procedures cannot make this differentiation on one examination alone. If, however, readings are obtained over a period of several weeks and comparison of them made, it is, in many cases, possible to tell whether it is only the conductive power of the nerve which is at fault, or the nerve has been divided completely.

Is it justifiable to wait until this differentiation can be made electrically? It is safe and the effects upon regeneration will not be jeopardized so far as we know

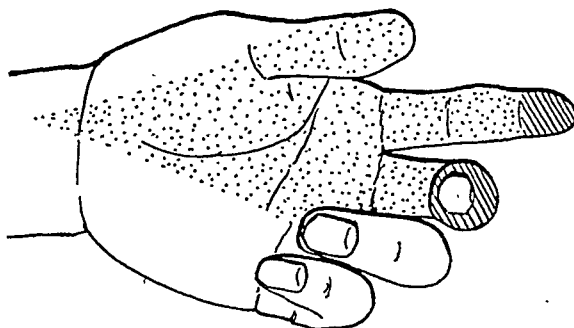


FIG. 3. Characteristic deformity for median nerve paralysis. Fingers are flexed. Note position of thumb—paralysis of abductor pollicis brevis. Diagonal lines—constant area of anesthesia for pin prick. Dotted area—usual area of sensory loss.

at the present time, if this can be determined in a period of from three to four weeks. Should it be impossible to tell at the end of four weeks, the nerve should be exposed surgically.

### PROBLEMS OF NERVE REPAIR

Primary repair, that is, suture of the nerve as soon after the injury as possible, is practiced by all surgeons and should be done where the injury is caused by sharp objects, such as a knife or piece of glass. When the injury is caused by a blunt object, bullets or shell fragments (in other words, when the nerve is torn apart) there is good evidence from the experiences during the war, to justify the practice of delayed repair. By this is meant that the nerve lesion is explored and sutured two to four weeks after the injury. At this time, it is possible to differentiate between the normal and the damaged nerve tissue with greater ease and certainty than several hours after the injury. This insures the removal of all damaged nerve tissue which, if left behind, may cause the formation of a neuroma and prevent the nerve from



regenerating. Furthermore, it enables the surgeon to remove the smallest amount of nerve tissue.

End-to-end suture, where the sutures are placed in the sheath of the nerve only, remains the most satisfactory form of repair. Both silk or tantalum wire may be used as suture material for there is no definite evidence that one is better than the other. The method of plasma-clot suture introduced by Young and Medawar of England and modified by Tarlov and Benjamin in this country may replace the material just mentioned. Before very long, sufficient evidence will have been compiled to permit a comparison of the results of the two methods. The plasma-clot suture is performed by laking plasma and allowing it to clot about the nerve ends after they have been placed end-to-end in a special mould. The resulting clotted plasma cuff holds the ends together firmly if no tension is necessary to keep them in position.

During the war, tantalum foil was wrapped about the suture site for the purpose of preventing scar tissue from growing between the nerve ends or choking the nerve. This practice has been abandoned because it has been found that, when the foil was removed, the nerves were encased in a fibrous membrane which had, in most instances, choked the nerve and prevented it from regenerating.

Nerve grafting has been shown definitely by various British and American workers to be unsatisfactory for guiding nerve axones across gaps in the nerve which cannot be overcome by the methods of re-routing the nerve and placing the extremity in that position which will relax it as far as possible. A great many methods have been used for preserving cadaver grafts and immediate transfer has been done from the fresh cadaver or the nerves have been obtained from a freshly amputated leg. Recently there has appeared in the literature the results of animal experimental work performed by Weiss and Taylor which show that bridging artificially made nerve gaps by a cylindrical blood clot sheathed by sleeves of artery or collagen tubing will permit the new axones growing from the proximal stump to find and follow the distal nerve stump to their terminal ends in the muscle. These workers have also obtained clinical evidence of regeneration by fastening firmly between the ends of the nerve a fiber glass cable, encasing it with blood clot and covering the entire preparation with a collagen tube. These experimental studies have yet to be given clinical trial.

#### PROBLEMS OF POSTOPERATIVE MANAGEMENT

After the nerve injury has been repaired, there are three principles which must be followed closely to

give the nerve an optimum opportunity to regenerate. They are:

1. Maintain the paralyzed muscles, anesthetic skin area and involved joints in top physical condition until regeneration is complete.
2. Prevent the paralyzed muscles from becoming overstretched and the development of deformities.
3. Sustain the patient's morale and, incidentally, your own interest.

As a result of nerve paralysis, the supplied muscles undergo atrophy, the affected joints may become ankylosed and the anesthetic skin may undergo trophic changes. These sequelae must be prevented as far as is possible until the nerve supply has been restored. To accomplish this, these patients should be placed on a regular regime of physical therapy treatments. These consist of the use of dry and/or moist heat, the latter in the form of whirlpool, and massage to the paralyzed muscles by a competent physical therapist. In the beginning, these treatments should be daily and later, as the patient becomes more active and has learned the care of the part, they may be given three times a week. To this may be added electrical treatments but here, great care must be exercised because there is no better way to exhaust paralyzed muscles than by the incorrect use of electrotherapy. For this reason, a physical therapist who has had experience with electrotherapy should be entrusted to administer it. As power returns, the patient is taught directional exercises, that is, specific exercises of the weak muscles, which are performed at regular intervals each day. As soon as the patient is capable, he is required to do that type of occupational therapy which will encourage the use of the involved muscles.

During all this time, the affected joints are kept freely movable by passive exercise. The anesthetic skin should at all times be kept clean, free from irritation and protected against pressure and burning.

For the purpose of preventing paralyzed muscles from becoming overstretched, a factor which inhibits the return of function, the affected part of the extremity as is indicated, is placed in a removable splint. Please do not consider this splint like that which is applied for the immobilization of fractures. It should be removed often, especially during periods of activity. It must be removed when giving physical therapy treatments but must always be worn during sleep.

Sometimes it is necessary to maintain the extremity in a certain position to keep the suture line from pulling apart by applying a fixed cast. This cast is removed by the surgeon at weekly or two-week intervals and replaced by a new one in a position of greater extension. By the end of six to eight weeks, this type



of fixation is no longer necessary and physical therapy treatments are started at once. At the same time, a movable cast as described above is applied, if it has not already been.

The regeneration of nerves takes anywhere from six months to two years, depending on the location of the injury to the innervated muscles. This is a long time. The interest of the patient may wane and I have seen mild depression result, especially when the nerve is essential for a well-functioning hand and is vital to the patient's livelihood. At the same time, the physician who is in charge of the patient may relax his vigilance over supervising the treatment. These factors, which may appear unimportant, are just as vital to the success of the repaired nerve as the surgery itself. Always maintain a hopeful attitude while managing your patient and, under no circumstances express doubt that the nerve will regenerate.

As a barometer for nerve regeneration we have the physical signs of improvement in color and texture of the skin, filling out of the shrunken paralyzed muscles, return of movement and sensation. In addition to these signs, we have the assistance of electrical examination to which I have referred when discussing the differential diagnosis of anatomic and physiologic interruption. Electrodiagnosis has a distinct value in following the progress of nerve regeneration, because it will show the reinnervation of the paralyzed muscles by the new motor neurones before the patient can voluntarily contract the muscles. This examination should be considered part of the treatment and be made at monthly intervals.

Although new electrodiagnostic methods have been introduced, those which have been found to be particularly valuable have not as yet come into general use. The determination of skin resistance in areas of sensory loss by a rather simple apparatus has been found to have only a qualitative value. It cannot be used for quantitative studies so that it is not useful in following regeneration. Probably the best method for the study of regeneration is the apparatus devised by F. H. Lewey and F. E. Nulsen. The apparatus is extremely simple and provides direct reading by the introduction of two needles into the nerve at any point distal to the repair. The results are direct in that the muscle contracts or does not, thus avoiding the plotting of complicated charts. Because the current is introduced into the nerve itself, it is probably more sensitive than other methods. However, until these new methods have become established, the use of galvanic and faradic stimulation, as well as chronaxie, should be used since they provide the information that is necessary for the successful management

of these lesions, even though they are at times difficult to interpret.

### PAIN

There are two types of pain which may result from peripheral nerve injuries. The first of these is that caused by irritation and is probably the result of the inflammatory process set up by the trauma. It is referred to by some writers as *minor causalgia*. The pain is usually burning, confined to the site of injury but may be referred to the distribution of the nerve and it is increased by movements which produce a pull on the site of injury and by pressure on, or around the area of wounding. Repair of the nerve in most patients will relieve it. Sometimes it continues for six to eight weeks after the nerve has been sutured and then disappears. If it does not, injection of the sympathetic ganglia which control the part involved, will relieve the pain.

The second type of pain is *causalgia*, which is an excruciating burning pain. The patient sits alone in agony, holding absolutely motionless the wet, cold hand or foot covered with a cloth, since movement, a gust of air or noise may cause an exacerbation of the pain. The hand or foot undergoes trophic changes and becomes "frozen" with contractures. The pain is most commonly associated with minor lesions of the peroneal and median nerves and it is these nerves which contain the largest component of sympathetic nerve fibers. Injection of the sympathetic ganglia or their removal has been found to completely relieve causalgia in many of these patients. This therapy must be done early in the course of the complaint, otherwise, it may be ineffective.

### RESULTS

There seems to be a general impression in the medical profession that nerve repairs are not very satisfactory. This is not true. As yet, there are no reports about the success of the treatment of nerve injuries during this past war because sufficient time has not elapsed to determine this fact. But the men who have been able to follow these patients are quite enthusiastic about the results they have seen. If the results of war injuries are good, there is more reason to be optimistic about civilian nerve injuries. The latter are, in many instances, less severe. Even though this were not true, the important fact is that in civilian practice these patients can receive individual post-operative management. This alone, providing the surgery has been done carefully, will do more toward maintaining the health of the affected muscles, joints and skin so that when they are reinnervated, they can perform their normal function.

# Clinical Physiology of Infectious Diseases of the Liver

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*An understanding of liver physiology is necessary to interpret properly the signs and symptoms of hepatic disease. In this article the author correlates the various disturbances in liver function with clinical manifestations and functional tests currently used in infectious diseases of the liver.*

Consideration of the clinical physiology of infectious diseases of the liver warrants a brief review of the normal anatomy and functions of the human liver. The anatomic and functional unit of the liver is the hepatic lobule, from the periphery to the center of which rows of liver cells are radially arranged. The mixed blood from the interlobar branches of the hepatic artery and portal vein courses through the liver capillaries or sinusoids (which are lined by endothelium and reticulo-endothelial or Kupffer cells) to the central vein of the lobule. The bile canaliculi or capillaries conduct bile from the more central regions of the lobule to the periphery where the bile is emptied into ramifications of the biliary tract. On one side, each row of hepatic cells is in contact with a blood capillary and on the other side with a bile capillary. The hepatic cells, therefore, are strategically placed so that they can receive substances from the blood stream and secrete others into the blood or into the biliary tract.

The many functions of the liver may be divided into four groups; viz., secretion of bile, metabolic activities, reticulo-endothelial functions, and circulatory functions. (A) Bile is a secretion insofar as it contains the bile salts (formed by the hepatic cells) which are so important to the small bowel in the digestion and absorption of fats and in the absorption of the fat-soluble vitamins D, K, and E, and carotene (pro-vitamin A). Bile is an excretion insofar as it serves as a medium for the removal of bilirubin (formed by the reticulo-endothelial cells generally of the body), urobilinogen (a bilirubin derivative), cholesterol and lecithin, and certain dyes and drugs when the latter are introduced into the body.

(B) The hepatic cells perform a number of metabolic functions the most important of which are: (1)

A highly significant role in carbohydrate metabolism, storing glucose as glycogen (glycogenesis), converting levulose and galactose to glucose, and converting lactic acid, glycerol, and deaminized amino acid radicals to glucose (gluconeogenesis). The liver also supplies glucose to the blood stream as needed (glycogenolysis).

(2) The liver likewise plays an important role in fat metabolism, desaturating fatty acids and thereby rendering them more oxidizable and utilizable by the body tissues, forming ketone bodies, and storing fat and fat-like substances. (3) The liver plays numerous roles in nitrogenous metabolism, including the formation and deamination of amino acids, and the formation of urea (and perhaps uric acid), plasma proteins (especially albumin and fibrinogen), prothrombin, hemoglobin, and also heparin and histamine. (4) The liver stores the hematopoietic or antipernicious anemia principle which appears now to be related to the B<sub>12</sub> complex vitamin, folic acid. (5) The liver also stores appreciable quantities of vitamins A, B group, and D, and converts carotene to vitamin A. (6) The liver has an important detoxication function, conjugating benzoic acid with glycine to form hippuric acid, inactivating the steroid hormones and the absorbed products of intestinal putrefaction through conjugation, and detoxifying certain drugs.

(C) The Kupffer cells, in common with other reticulo-endothelial cells, are important in bilirubin formation, the storage of iron and copper, antibody formation, and phagocytosis.

(D) The liver constitutes the portage area for the blood returning to the right heart from the splanchnic region and aids in the regulation of blood volume, and the water and electrolyte balance of the body.

Liver function tests are obviously of much clinical significance in the differential diagnosis, evaluation and prognosis of liver diseases, including infectious diseases of this organ. These tests fall into two classes; viz., those which test the excretory functions of the liver and those which test various of its metabolic functions. (A) Excretory function tests include (1) the icterus index, (2) the van den Bergh (serum bilirubin determination), (3) urinary and fecal bile pigment determinations, (4) the bilirubin tolerance

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test, and (5) urinary urobilinogen determination. All of these evaluate the ability of the liver to excrete bilirubin or its derivatives into the bile. (6) The bromsulphalein test measures the ability of the liver to excrete this dye into the bile. (7) The determination of the alkaline serum phosphatase level is believed to measure the capacity of the liver to excrete this enzyme into the bile.

(B) There are a number of tests for the metabolic functions of the liver. (1) The glucose, levulose, and galactose tolerance tests measure the ability of the hepatic cells to store glucose as glycogen and to transform levulose and galactose into glucose. (2) The determination of the plasma cholesterol (total, free and esterified) affords some measure of the metabolic functions of the liver in relation to fatty substances. (3) The determination of the plasma proteins (total, albumin, globulin, and fibrinogen, and A/G ratio) measures the ability of the liver to form these proteins, particularly albumin and fibrinogen. (4) The cephalin flocculation test probably involves the plasma protein formation function of the liver, since abnormal cephalin flocculation on mixture of the cephalin solution with the serum of a patient with liver disease is probably linked with changes in the plasma globulins. (5) The prothrombin time, of course, measures the ability of the liver to form this important blood clotting factor for which vitamin K is necessary. (6) The hippuric acid test, as previously indicated, is a measure of the detoxifying function of the liver.

Of these tests the most frequently used clinically are bilirubin determinations on the blood (van den Bergh) and urine, the bromsulphalein test, the galactose tolerance test, the determination of the plasma proteins (including the A/G ratio), the cephalin flocculation test, the prothrombin time, and the hippuric acid test. Because the liver has so many functions, no less than three or four of these tests involving both the excretory and metabolic functions of the liver should be employed in evaluating its functional capacity in disease. These tests are helpful in differentiating between hepatogenous, intrahepatic or "medical" jaundice and obstructive, extrahepatic or "surgical" jaundice but they cannot be substituted for a thorough history, a searching physical examination, and diagnostic acumen.

In considering the clinical physiology of infectious diseases of the liver, the facts relative to liver reserve and capacity for regeneration should be recalled. In the experimental animal, deficiencies in liver function and abnormal function tests are found only after approximately 80 per cent of normal liver tissue has been removed surgically. The liver of a normal man

also has a large reserve, so that our moderately sensitive liver function tests detect only extensive interference with liver physiology. Fortunately also, the liver has great regenerative capacity as evidenced by the fact that following surgical removal of 80 per cent of the liver from the normal experimental animal, the liver regains its original size after only a few months.

There obviously are many similarities between alterations in the physiology of the liver produced by different infectious diseases involving this organ, including infectious hepatitis, homologous serum jaundice, malaria, amebiasis, Weil's disease, yellow fever, infectious mononucleosis, brucellosis and other infections, suppurative and otherwise. In recent years, however, the most extensive studies of altered liver physiology have been made in relation to the two virus infections, infectious or epidemic hepatitis (a newer name for catarrhal jaundice) and homologous serum jaundice. Rarely an infectious disease of the liver may result in massive liver necrosis with acute and fatal failure of liver functions over a period of several weeks, resembling somewhat the more rapid death (24 hours) of dogs and other animals following total hepatectomy. Fatality in man results not only from failure of liver function but also from the absorption of toxic split protein products released into the blood and lymph streams from the massively necrosing liver. More often, however, in infectious diseases of the liver there is cloudy swelling of the hepatic cells, necrosis of some liver areas and inflammatory exudate into the periportal regions, with reduced functional efficiency of the liver. The edema, inflammatory reaction and circulatory congestion produced by liver infections account for the hepatomegaly frequently present. The circulatory congestion causes a certain degree of liver anoxia which also interferes with liver functions. The hepatic tenderness which may be present is due mainly to the stimulation of somatic pain fibers in the stretched peritoneal attachments and adjacent parietal peritoneum where areas of local peritonitis may be present, as well as to stimulation of visceral pain fibers by distension of intrahepatic vascular and biliary tract radicles. The splenomegaly which may be present results in the main from portal congestion, as does ascites when it occurs. Partial obstruction to the portal blood flow also accounts for the hyperemia and edema of the gastro-intestinal tract. The resulting altered motility of the stomach and gut with changes in the nerve impulses passing up the vagi and splanchnics to the brain accounts in part at least for the symptoms of anorexia, nausea, and abdominal discomfort and pain.

The jaundice which is usually present in infectious diseases of the liver, is, of course, due partially to the decreased ability of the damaged liver cells to excrete bilirubin into the biliary passages and partially to incomplete obstruction of the smaller biliary tract radicles by the inflammatory process with resulting reabsorption into the blood stream of excreted bilirubin. As a consequence there is an increased concentration of this pigment in the blood and tissues. The dark urine and light-colored stools frequently present are, of course, accounted for on the basis of abnormal excretion of bile pigment into the urine and decreased excretion of bile pigment via the common bile duct into the small intestine. Increased urinary urobilinogen is frequently seen due to decreased ability of the liver to excrete this bilirubin derivative into the bile after its absorption into the blood stream from the lower intestinal tract. Since the excretory functions of the liver are interfered with, the bromsulphalein dye test (which cannot be performed satisfactorily in the face of a heavily jaundiced plasma) frequently shows delayed excretion of the dye into the biliary tract and therefore increased retention in the blood stream. The alkaline serum phosphatase is frequently increased due presumably to decreased excretion of this enzyme via the bile. Decreased formation of bile acids by the damaged hepatic cells and decreased excretion of the bile salts formed due to partial intrahepatic biliary obstruction, results in a deficiency of bile salts in the small bowel and consequently an interference with the normal digestion and absorption of fats. Tolerance to this class of foodstuff is therefore reduced. The deficiency of bile salts in the small bowel also interferes with the absorption of the fat-soluble vitamins, of which vitamin K ordinarily is clinically the most important. Reabsorption of bile salts from the partially obstructed intrahepatic biliary radicles may increase the bile salt concentration of the blood. This is thought by some to be responsible for the bradycardia sometimes seen in liver disease, the action presumably being on the vagus. The pruritus which may be present is also thought by some to be due to the action of bile salts on the peripheral pain and other nerve endings in the skin. There is some evidence indicating a toxic action of the bile salts on the central nervous system which may account in part for the tremor and other nervous signs and symptoms which sometimes are present.

The physiology of the liver in relation to metabolic functions is likewise altered. Thus the role of the liver in carbohydrate metabolism is defective as evidenced by decreased ability to form glucose from

levulose and galactose and to store glucose as glycogen. This can be demonstrated by abnormal galactose, levulose, and glucose tolerance tests. Adequate glycogen stores in the liver are known to protect this organ against various toxic agents so that its defective carbohydrate metabolism acts as part of a vicious cycle. Decreased ability of the liver to perform its normal role in fat metabolism may be demonstrated by an increase in the ratio of the free to total cholesterol of the plasma and by an increase in the plasma lipids and phospholipids. Decreased efficiency of the liver in protein metabolism may be demonstrated by decreased plasma protein formation evidenced particularly by a fall in the serum albumin and a decrease in the A/G ratio. Prothrombin production by the liver cells in the more severe types of liver involvement may be sufficiently interfered with (as demonstrated by a prolonged prothrombin time) to be responsible for petechial and other hemorrhages into the skin, mucous membranes, and other tissues. Increased capillary permeability resulting from the release of histamine and other toxic substances from the damaged liver may also play a role in the production of these hemorrhages. In patients showing a prolonged prothrombin time, the failure of the parenteral administration of vitamin K to stimulate increased prothrombin formation is an unfavorable prognostic sign. Adequate protein stores in the liver, like adequate glycogen stores, serve to protect the organ against noxious agents, whereas increased fat appears to have an opposite effect. Changes in the plasma proteins produced by liver involvement are probably responsible, as previously stated, for the frequent finding of a positive or abnormal cephalin flocculation test which has proved to be a relatively sensitive indicator of liver damage (even though the mechanism of the test is still poorly understood).

Anemia is not a common sign in infectious diseases of the liver, although it sometimes occurs. When macrocytic, the character of the anemia is probably related to interference with the normal storage and action of the hematopoietic liver principle. The mechanism of the modest leukopenia which may be present in virus infections of the liver is not understood, although interference with folic acid storage and action is a possibility. Deficiencies in the intestinal absorption and liver storage of certain vitamins may occur. Vitamin K has already been mentioned. The B complex vitamins are also important, particularly since two members of this group (choline and inositol) are known to have a protective action against fatty livers. The detoxifying function of the hepatic cells is decreased in infectious diseases in-

volving this organ and this deficiency may be demonstrated by the hippuric acid test (which is more sensitive when performed intravenously rather than orally).

In closing, it should be emphasized that because of the many functions of the liver and because they may be affected differentially by infectious diseases of the organ, observations and tests of several liver functions should be made. Repetition of such observations and tests is valuable in following the course of the disease and its prognosis. Even though the results of liver function tests may have returned to normal values, liver regeneration and repair may still be in process, since these tests are only moderately sensitive. Hence such signs as reduced exercise tolerance and ease of fatigue are valuable in suggesting that convalescence

is still proceeding. If the complaints of the patient suggest a recrudescence of the infection, liver function tests are valuable in demonstrating whether a reactivation of the inflammatory process has actually taken place. Finally, a sound understanding of the pathophysiological processes of infectious diseases of the liver constitutes the most effective basis for future advances in therapy.

#### GENERAL REFERENCES

- Best, C. H., and N. B. Taylor: *Physiological Basis of Medical Practice*, ed. 4, Baltimore, Williams & Wilkins, 1945.  
Wiggers, C. J.: *Physiology in Health and Disease*, ed. 4, Philadelphia, Lea & Febiger, 1944.  
Nash, J.: *Surgical Physiology*, Springfield, Thomas, 1942.  
Levinson, S. A., and R. P. MacFate: *Clinical Laboratory Diagnosis*, ed. 3, Philadelphia, Lea & Febiger, 1946.

#### The Koch Phenomenon

I shall begin my pursuit of understanding by referring to the Koch phenomenon. I remember learning about this interesting historical relic as a student, without ever realizing how much it explains. You remember that Koch injected a healthy guinea-pig with a pure culture of tubercle bacilli. This resulted in a local inflammation at the site of inoculation and enlargement of the regional lymph glands. After an interval of four to six weeks the animal was reinoculated, necrosis took place at the site of the inoculation, but the related glands did not enlarge and general infection did not ensue. The bacilli tend to become fixed at the site of local necrosis, which heals rapidly. It is no mere picturesque description to point out that, in gazing at this necrosis, Koch viewed the sacrifice of the local tissue to rid the host of the reinfecting bacilli. One may generalize, therefore, and say that it is a part of the Koch phenomenon that, on reinfection, the local organ sacrifices itself so that the body may be protected from bacillary invasion and live. The truth of this is nowhere better shown than in the lung. I shall show some films of primary infection in the lungs with the lesion at the site of inoculation and enlargement of the related glands. I shall show many of the reinfection type, in which there is destruction in the lung and no gland enlargement and no systemic disease.

People are fond of reiterating that pulmonary tuberculosis is but part of a systemic disease. This is an unhelpful and indeed a wrong conception. The whole meaning of the struggle that goes on in the lung is but a counterpart of the phenomenon observed by Koch in the skin of the guinea-pig. Even the cavity is seen in this light as a desperate effort to rid the lung of infection. Surely on reflection it is staggering how even the grossest destruction of lung tissue may occur without dissemination of the infection, other than by direct spread to the larynx and the gastro-intestinal tract. On the basis of the Koch phenomenon some of the modern treatment of pulmonary tuberculosis finds its justification.

—C. H. Fitts, *The Medical Journal of Australia*, 2:622 (Nov. 2) 1946.

# CASE REPORT . . .

## Atypical Pneumonia with X-Ray Findings Simulating Tuberculosis\*

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*This case report illustrates the importance of interpreting the results of special examination in the light of the data obtained by the clinician.*

The etiology and nature of pulmonary lesions can never be determined with certainty from the configuration and distribution of abnormal shadows on the x-ray plate. Error is especially apt to occur if tuberculosis is diagnosed on the basis of x-ray findings alone. The following report demonstrates how closely the shadows due to a relatively benign non-tuberculous lesion may mimic those due to pulmonary tuberculosis.

### CASE REPORT

C. J., a 20-year-old student nurse, was admitted to the otolaryngology service on September 17, 1946, complaining of sore throat, cough, malaise, and headache of 12 hours' duration. The onset of her present illness had been heralded by a short chill.

Her past health had been good. The Mantoux reaction had been negative in March 1946. Her only recent illness was a mild fungus infection of the palate, for which she had been hospitalized in August 1946. Culture of the lesions yielded a *Candida*, probably *C. albicans*, the organism of ordinary thrush. Prompt and complete healing occurred on local therapy. During this illness a chest x-ray (Fig. 1) revealed no abnormalities.

On admission she appeared to be acutely but not seriously ill. Temperature was 101° F., pulse rate 120, respiratory rate 20. The nasal and pharyngeal mucosa were reddened, the anterior cervical nodes palpable. No other abnormal findings were noted.

During the next three days the presenting symptoms continued. The temperature fluctuated daily between 98° and 102° F. She began to bring up small amounts of mucopurulent sputum. On Sep-

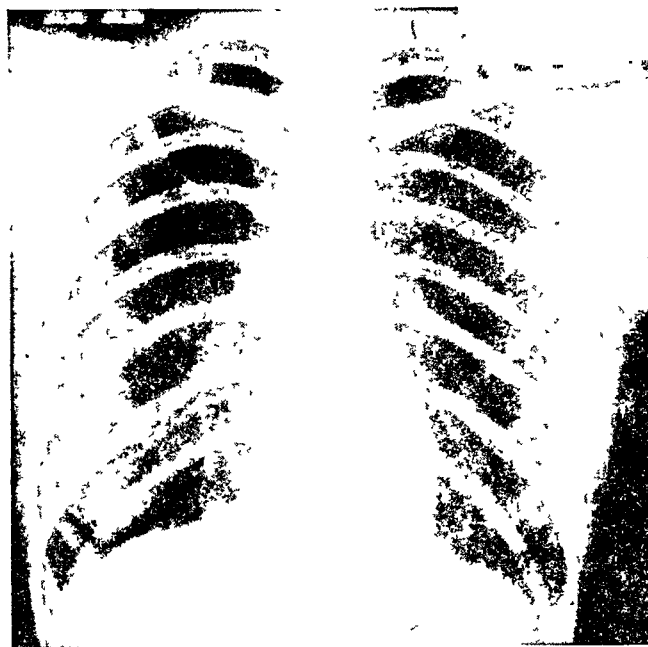


FIGURE 1

tember 20 we were asked to examine the patient because it was felt that she had trouble in her chest. Fine crackling râles were heard on the right side posteriorly above the spine of the scapula, but there were no abnormalities of the percussion sounds or breath sounds. An x-ray taken on this day (Fig. 2) showed infiltration in the right upper lobe, most marked near the medial portion, associated with slight upward displacement of the short interlobar fissure. The impression of the radiologist was "pneumonia vs. tuberculosis."

The blood picture was not helpful, the leukocytes numbering 8,700 with 64 per cent neutrophils, hemoglobin 13.2 Gm. or 88 per cent. Urine was normal. Five consecutive 24-hour sputum specimens, examined by the Pottenger concentration technic, were negative for tubercle bacilli. Mantoux tests, using consecutively stronger dilutions up to 1:100, were negative also. No fungi were found in the sputum.

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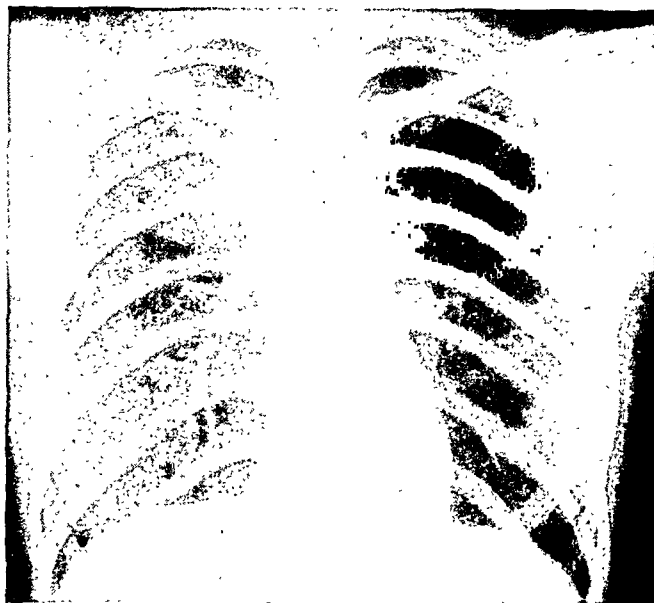


FIGURE 2.

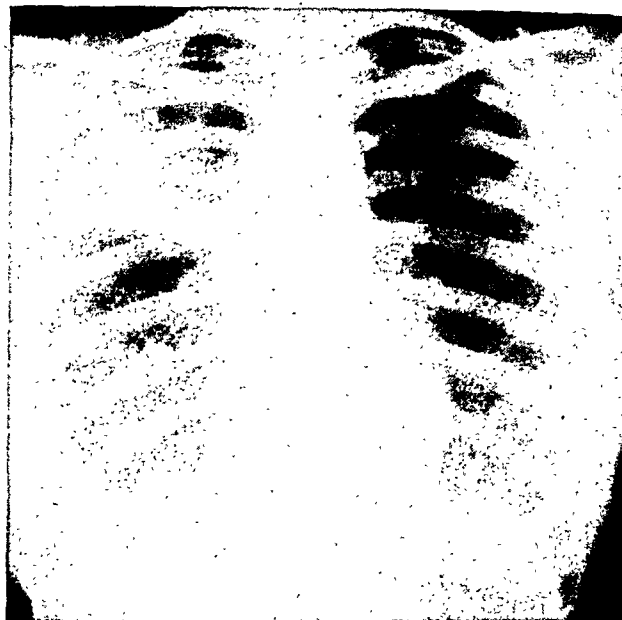


FIGURE 4.

On September 21 the temperature returned to normal and remained so thereafter. The patient continued to cough and to raise sputum for several days, however. The cough was frequent and annoying, but the sputum was relatively scant, never exceeding 30 cc. per day.

On September 25, the patient having been afebrile for four days, examination revealed dullness on percussion and almost complete absence of breath sounds

over the right upper lobe. On this day the x-ray (Fig. 3) showed considerable increase in the size and density of the area of infiltration, associated with more marked upward displacement of the interlobar fissure. Near the center of the area of infiltration was a region of decreased density which could be interpreted as suggestive of cavitation. This plate almost exactly simulates tuberculosis with cavitation and contraction of the right upper lobe. The similarity can be seen

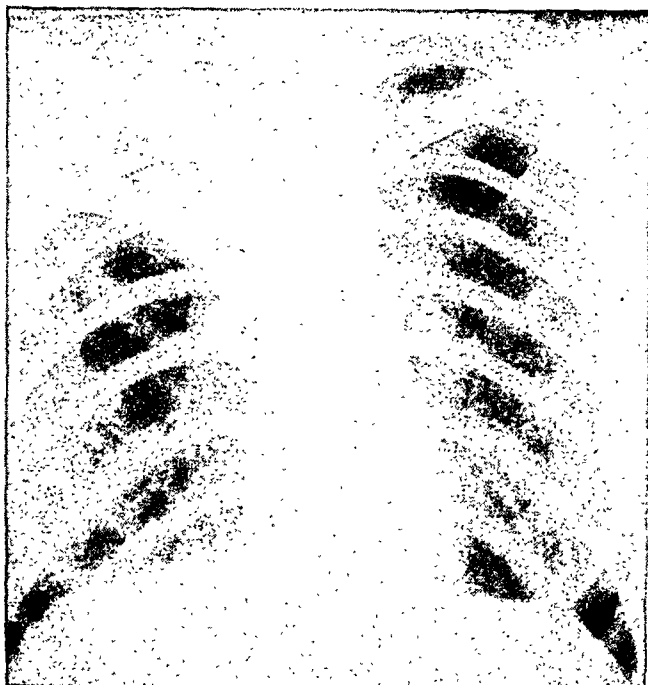


FIGURE 3.

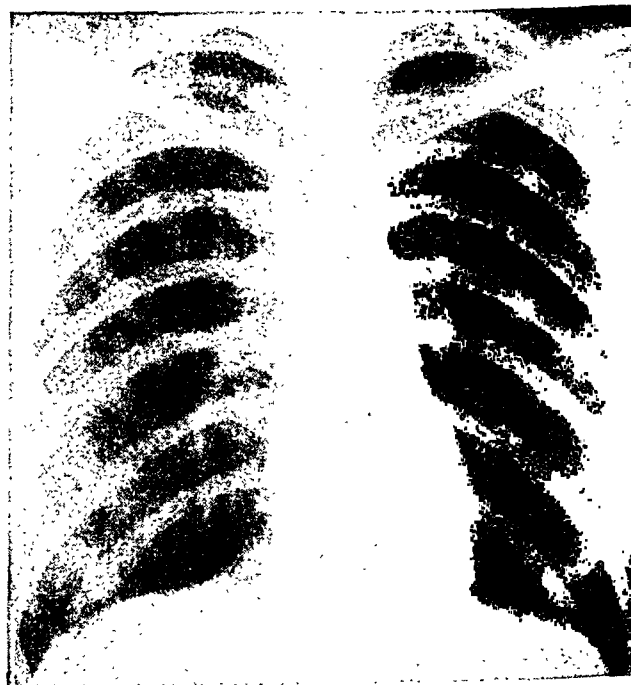


FIGURE 5.

by comparison with Figure 4, which is the chest plate of another patient with proved tuberculosis.

During the next week the cough and sputum gradually subsided, and the abnormal physical signs in the chest cleared. An x-ray taken on October 7 (Fig. 5), just before discharge, showed complete clearing of the pulmonary lesion.

## DISCUSSION

In this case of atypical pneumonia the simulation of the x-ray appearance of tuberculosis was undoubt-

edly due to atelectasis of the right upper lobe, which resulted from obstruction of branch bronchi by thick exudate. This case, we believe, emphasizes the importance, in clinical diagnosis, of the correlation of data obtained by several methods of study. The x-ray is superior to all other methods in determining the presence or absence of pulmonary lesions and their distribution, but it cannot determine etiology. Nor is it always possible, from the x-ray alone, to determine such factors as the acuteness or chronicity of lesions, and whether or not abnormal shadows represent fibrotic, productive, exudative, or excavating lesions.

## Medical Journalese?

I am going to start a one-man war against our chief occupational disease, though I cannot look forward to any Nobel award if I succeed. My only recompense will be in the fact that the medical profession are the chief sufferers. Slowly but surely this detestable complaint, jargon aphasia, eporrhoea, or Herbert's disease, has been invading our ranks from the chief endemic reservoir of infection—the official circular. Typical cases, like the "disinfestation officer" who circulated a report which suggested that mice should be trapped as they emerge from their apertures, are fortunately rare, but there is no lack of this kind of thing:

"This failure to exercise objective acumen derives from professional indoctrination with the time-worn diagnostic axiom, that to seek a plurality of causes for a clinical picture is deplorable. It is understandable that in a busy clinic, scientific curiosity may be curbed when the therapeutic exigencies are abbreviated by the self-determined course of the disorder. . . . The phenomenology observed following ingestion of *Datura stramonium* seeds may be incorrectly interpreted as evidence of an affective disorder."

"Pronation deficiency following immobilisation in plaster can be minimised by taking care to avoid inversion of the foot, and to see that the foot is pronated in plaster as much as possible."

"The drug is devoid of risk, but irresponsible patients should preferably be institutionalised."

In the general presence of disease we may forget the look of health. "Sir, your son was struck in the leg by a cannonball, that we were forced to cut it off, whereof he died. . . ." ". . . that you be hanged by the neck until you are dead, and the Lord have mercy on your soul." Deformed as we are, of necessity, by the weight of sulphonamides, heteroauxins, heteronymous hemianopias, and osteodystrophiae epiphysio-arthritiscae, we can at least raise our heads to look back at better days.

In the matter of words and units, the electricians, who made themselves a vocabulary to measure, have the better of us. Their terminology, crisp, homely, and readily transferable into an alphabet of signs that recall gardening implements, is enviable to us—better than the rings and semi-detached indoxyl penthouses of the biochemists with their barbarous names. Could we not measure olfactory thresholds in snouts and megasnouts, the lateness of honorary physicians at rounds in dawdles or coffees? A terminology rugged but not barbarous, that is what we want. Let us take personal names if we wish, and to ohms and curies let us oppose chaplins of valgus deformity, potts of curvature, even megafreddies of azoospermia and charringtons of polyuria. We could well enrich the language which we are now occupied to outrage.

—Peripatetic Correspondent, *The Lancet*, 251:806 (Nov. 30) 1946.



# Maintaining Nitrogen Balance with Amino Acids

## Four Adults Maintained by Acid Hydrolyzed Casein Fortified with One per cent dl-Tryptophane Given Orally

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*Current interest in the use of amino acid mixtures as an aid in the management of disease and injury makes it necessary to have knowledge of the amounts of the amino acid preparations necessary to maintain nitrogen equilibrium under various conditions. This paper shows the amounts which were adequate in two normal men. Of particular interest in relation to the practical application of such procedures is the reduction in nitrogen retention which occurred when the calory intake was lowered.*

Protein hydrolysates have been used orally and parenterally to augment the daily nitrogen intake.<sup>1,2</sup> Elman<sup>3</sup> and Shohl<sup>4</sup> were among the first to use a hydrolysate of casein by oral and parenteral administration as the sole source of nitrogen in equilibrium studies on human subjects. Altshuler<sup>5</sup> and also Curreri<sup>6</sup> have maintained adults in nitrogen equilibrium by venoclysis for periods of five to seven days. Abbot<sup>7</sup> maintained hospital patients in nitrogen equilibrium for periods of ten to twelve days by intravenous alimentation.

Long term balance studies by Rose<sup>8</sup> on human subjects have proved that a mixture of purified amino acids will maintain adults in nitrogen equilibrium; eight amino acids have been found to be essential.

Using acid hydrolyzed casein fortified with one per cent dl-tryptophane as the only source of nitrogen, Kade<sup>9</sup> has shown that dogs can be maintained in nitrogen balance by oral or parenteral alimentation. The following study was undertaken to determine if human adults could be maintained in nitrogen equilibrium for relatively long periods by the oral administration of acid hydrolyzed casein fortified with 1 per cent dl-tryptophane.†

\* From the Department of Pediatrics and Communicable Diseases, University of Michigan Medical School, Ann Arbor, Mich.

† We are indebted to Frederick Stearns and Company for aid in carrying out this work.

‡ Parenamine—Frederick Stearns and Company, Detroit, Mich. A 15 per cent solution of amino acids derived from the acid hydrolysis of casein and fortified with 1 per cent dl-tryptophane. The humin and excess minerals have been removed by special processes.

## METHODS AND ANALYSIS

Complete 24-hour-urine specimens were collected and preserved with 5 cc. toluene and 10 cc. of 50 per cent sulfuric acid. The nitrogen content of the urine was determined by macro-Kjeldahl analysis. The distillate was collected in boric acid and titrated with 0.14 N hydrochloric acid using the methyl red-bromocresol green indicator of Ma and Zuazaga.<sup>10</sup> Total creatinine of the urine was determined by an adaptation of the Folin method<sup>11</sup> as modified by Peters,<sup>12</sup> and the free amino acid nitrogen of the urine by the method of Albanese and Irby.<sup>13</sup>

All the feces were collected and analyzed, being preserved with dilute sulfuric acid and refrigeration until analysis could be done. They were prepared for analysis by the method of MacKay and Butler<sup>14</sup> and the total nitrogen determined by macro-Kjeldahl. For subjects 1 and 2 specimens were marked with carmine at three-day intervals and the three-day specimens pooled for analysis.

For subjects 1, 2 and 4 the dietary constituents were analyzed (macro-Kjeldahl) and the total nitrogen content of each diet calculated. For subject 3 aliquots

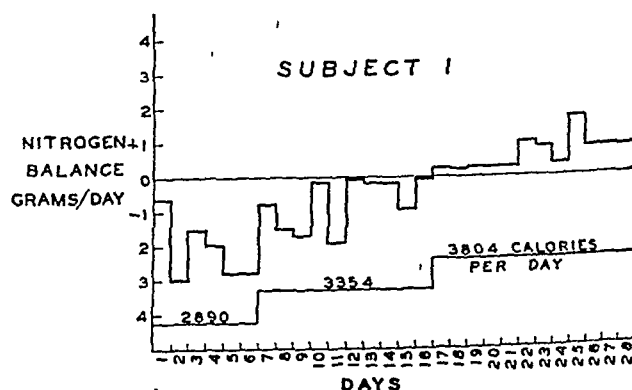


FIG. 1. A nitrogen balance study of a normal adult human for 28 consecutive days using as the sole source of nitrogen acid hydrolyzed casein fortified with one per cent dl-tryptophane.

TABLE I  
*Nitrogen Equilibrium—Subject 1 (75 kilo)*

DAYS	CALORIES	CREATININE	NITROGEN					
			AMINO ACID	URINE	FECES	TOTAL OUTPUT	INTAKE	BALANCE
		mg.	mg.	Gm.	Gm.	Gm.	Gm.	Gm.
1	2890	2000	654	12.28	0.697	12.98	12.36	-0.62
2	2890	2015	445	14.66	0.697	15.35	12.36	-2.99
3	2890	1876	349	13.19	0.697	13.89	12.36	-1.53
4	2890	2108	408	13.88	0.419	14.30	12.36	-1.94
5	2890	2129	430	14.71	0.419	15.13	12.36	-2.77
6	2890	2129	430	14.71	0.419	15.13	12.36	-2.77
Average daily nitrogen loss								-2.10
7	3354	2129	430	14.71	0.550	15.07	14.39	-0.78
8	3354	2040	468	15.35	0.550	15.90	14.39	-1.51
9	3354	1950	374	15.54	0.550	16.09	14.39	-1.70
10	3354	2004	387	13.85	0.662	14.52	14.39	-0.13
11	3354	2054	490	15.65	0.662	16.31	14.39	-1.92
12	3354	2062	350	13.80	0.662	14.46	14.39	-0.07
13	3354	2062	350	13.80	0.761	14.56	14.39	-0.17
14	3354	2062	350	13.80	0.761	14.56	14.39	-0.17
15	3354	1887	426	14.55	0.761	15.31	14.39	-0.92
16	3354	1879	523	13.49	0.983	14.47	14.39	-0.08
Average daily nitrogen loss								-0.75
17	3804	1896	444	13.19	0.983	14.17	14.39	+0.22
18	3804	1933	450	13.62	0.983	14.60	14.39	+0.21
19	3804	1914	460	13.58	0.587	14.17	14.39	+0.22
20	3804	1914	460	13.58	0.587	14.17	14.39	+0.22
21	3804	1914	460	13.58	0.587	14.17	14.39	+0.22
22	3804	2064	658	12.50	0.903	13.40	14.39	+0.99
23	3804	1811	421	12.68	0.903	13.58	14.39	+0.81
24	3804	1896	460	13.17	0.903	14.07	14.39	+0.32
25	3804	1799	500	11.74	0.959	12.70	14.39	+1.69
26	3804	1864	645	12.64	0.959	13.60	14.39	+0.79
27	3804	1864	645	12.64	0.959	13.60	14.39	+0.79
28	3804	1864	645	12.64	0.959	13.60	14.39	+0.79
Average daily nitrogen retention								+0.61

of a complete day's diet were analyzed. The diets were prepared by emulsifying the corn oil with agar or gelatin, and the sugar, salts and protein thoroughly mixed with the emulsion in a Waring Blendor.

All chemical determinations were run in duplicate.

#### EXPERIMENTAL OBSERVATIONS

The nitrogen equilibrium of two normal adults and two hospital patients receiving a synthetic diet of Parenamine, glucose and corn oil was studied. Vitamins § and minerals ¶ were provided. No attempt

§ Subjects 1, 2 and 3 received one vitamin capsule/day (Bio-mines—Frederick Sterns & Co.) containing Vit. A—5,000 U.S.P. units; Vit. D—800 U.S.P. units; thiamine hydrochloride—2 mg.; riboflavin—3 mg.; ascorbic acid—75 mg.; niacinamide—25 mg.; liver concentrate 1:20—80 mg.

Subject 4 received 10 cc. of a Solu-B preparation/day contain-

ing thiamine—50 mg.; riboflavin—20 mg.; pyridoxin—10 mg.; Ca pantothenate—100 mg.; niacinamide—1 Gm.; chlorobutanol—50 mg.

¶ Subjects 1 and 2 received 12 Gm. of salt mixture/day (Jones and Foster<sup>25</sup>). Subject 3 received 20 Gm./day.

Subject 4 received 250 cc. Ringers solution per day from the 4th through the 17th day. For the 18th through the 22nd day 12 Gm./day of salt mixture<sup>25</sup> were given.

#### EXPERIMENTAL HISTORIES

Subject 1 was a healthy male medical student (aged 25). He received the synthetic diet for 28 consecutive days. The nitrogen was supplied by the oral administration of Parenamine. The compositions of the

ing thiamine—50 mg.; riboflavin—20 mg.; pyridoxin—10 mg.; Ca pantothenate—100 mg.; niacinamide—1 Gm.; chlorobutanol—50 mg.

¶ Subjects 1 and 2 received 12 Gm. of salt mixture/day (Jones and Foster<sup>25</sup>). Subject 3 received 20 Gm./day.

Subject 4 received 250 cc. Ringers solution per day from the 4th through the 17th day. For the 18th through the 22nd day 12 Gm./day of salt mixture<sup>25</sup> were given.

TABLE II  
*Nitrogen Equilibrium—Subject 2 (77 kilo)*

DAYS	CALORIES	CREATININE	NITROGEN					
			AMINO ACID	URINE	FECES	TOTAL OUTPUT	INTAKE	BALANCE
		mg.	mg.	Gm.	Gm.	Gm.	Gm.	Gm.
1	3864	1850	347	14.68	0.576	15.26	16.53	+1.27
2	3864	1844	240	14.16	0.576	14.74	16.53	+1.79
3	3864	2095	400	15.86	0.576	16.44	16.43	-0.01
4	3864	2052	468	15.91	0.628	16.54	16.36	-0.18
5	3864	2230	563	16.53	0.628	17.16	16.37	-0.79
6	3864	2145	390	16.70	0.628	17.33	16.33	-1.00
7	3864	2261	396	17.04	0.628	17.67	16.41	-1.26
8	3864	1736	182	10.84	0.859	11.70	10.72	-0.98
9	3864	2033	461	14.63	0.859	15.49	16.41	+0.92
10	3864	1999	415	14.20	0.859	15.06	16.41	+1.35
11	3864	1894	373	14.26	0.668	14.93	16.41	+1.48
12	3864	1969	421	15.01	0.668	15.68	16.41	+0.73
13	3864	2160	439	15.61	0.668	16.28	16.35	+0.07
14	3864	2154	433	15.02	0.631	15.65	16.35	+0.70
15	3864	1964	430	13.98	0.631	14.61	13.37	-1.24
16	3864	1824	331	12.69	0.631	13.32	16.35	+3.03
17	3864	1972	350	13.76	0.631	14.39	16.35	+1.96
18	3864	1872	355	13.53	0.614	14.14	16.37	+2.23
19	3864	2075	444	15.73	0.614	16.34	16.41	+0.07
20	3864	2021	403	14.23	0.614	14.84	16.41	+1.57
21	3864	2225	447	13.44	0.700	14.14	16.41	+2.27
22	3864	1619	348	11.97	0.700	12.67	13.54	+0.87

Average daily nitrogen retention +0.68

diets are contained in Table V. In addition to this diet the subject received 200 cc. of grapefruit juice daily. Nitrogen other than that provided by the amino acids did not exceed 200 mg./day. The subject did not object to the diet. Normal daily activity was continued throughout this period, and although extremely active, he experienced no ill-effects from this regime.

The data for subject 1 are presented in Table I and Figure 1. The subject estimated that his usual caloric intake was approximately 3,000 Cal./day. For the first six days, therefore, the diet contained 2,890 Cal./day (38.5 Cal./kilo) and 12.15 Gm. of nitrogen. Because the subject was in negative nitrogen balance during this period, showing an average loss of 2.10 Gm. of nitrogen per day, the nitrogen and caloric content of the diet were increased to 3,354 calories (44.7 Cal. per kilo) and 14.18 Gm. of nitrogen per day (191 mg. per kilogram of body weight) for the following ten days. The subject remained in negative nitrogen balance but the average daily loss of nitrogen was reduced to 0.75 Gm./day. For the remaining twelve days the caloric content of the diet was increased to 3,804 Cal./day (50.7 Cal./kilo); the nitrogen content remained the same. The subject went into positive balance immediately and remained

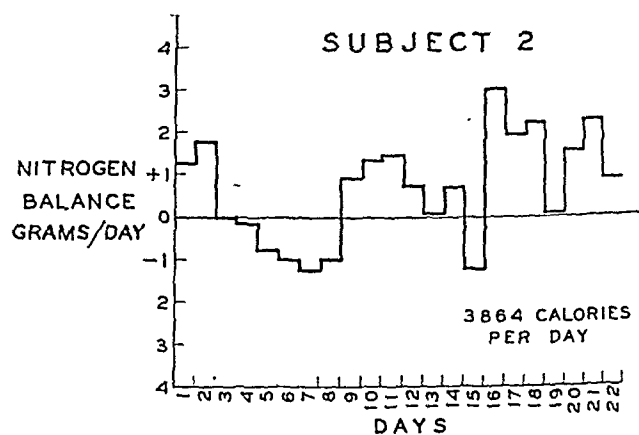


FIG. 2. A nitrogen balance study of a normal adult human for 22 consecutive days using as the sole source of nitrogen acid hydrolyzed casein fortified with one per cent dl-tryptophane.

in positive balance for the entire twelve days; the average daily retention of nitrogen for this period was 0.61 Gm.

Subject 2, a normal adult man (aged 22), was a hospital laboratory assistant, and, in addition, delivered 800 newspapers each morning before work. For 27 consecutive days he received a synthetic diet, the nitrogen content of which was supplied by the oral administration of Parenamine. The composition of the

TABLE III  
*Nitrogen Equilibrium—Subject 3 (57 kilo)*

DAYS	CALORIES	CREATININE	NITROGEN					
			AMINO	URINE	FECES	TOTAL	INTAKE	BALANCE
			ACID			OUTPUT		
		mg.	mg.	Gm.	Gm.	Gm.	Gm.	Gm.
1	3432	954	254	5.29	6.82	12.11	14.62	+2.52
2	3432	832	439	5.95	5.56	11.51	14.62	+3.11
3*	3432	530	142		7.67		14.62	
4*	3432	780	106		7.67		14.62	
5	3432	992	293	5.52	3.86	9.83	14.62	+5.24
6	3432	879	353	5.38	7.02	12.41	14.62	+2.21
7	3432	991	552	6.88	7.26	14.14	14.62	+0.48
8†	3432	994	288	6.06			14.62	
9‡	3432	983	350	6.02	6.40	12.42		
Average daily nitrogen retention								+2.71
10	3468	879	310	6.34	4.29	10.63	15.58	+4.95
11‡	3468	874	656	9.53	4.29	13.82		
12	3468	1051	270	10.07	4.81	14.88	15.58	+0.70
13	3468	980	460	10.01	4.81	14.82	15.58	+0.76
14	3468	955	539	10.55	4.12	14.67	15.58	+0.91
15	3468	980	546	9.50	3.33	12.83	15.58	+2.75
16	3468	1039	345	9.01	3.33	12.34	15.58	+3.24
17	3468	911	436	9.60	4.88	14.48	15.58	+1.10
18	3468	911	436	9.60	4.88	14.48	15.58	+1.10
Average daily nitrogen retention								+1.94

\* Incomplete urine.

† No data for stool.

‡ Incomplete intake.

diet is shown in Table V. In addition to this diet he received grapefruit juice, varying from 80 to 350 cc. daily. Nitrogen other than that provided by the amino acids did not exceed 340 mg./day. This subject objected to the taste of the diet and on a few days experienced some difficulty in retaining it.

The data for subject 2 are presented in Table II and Figure 2 for 22 days only because the collection of feces for the first five days was not accurate. He received 3,864 Cal./day (50 Cal./kilo) and 16.4 Gm. of nitrogen (211 mg. per kilogram of body weight) at which level the average daily nitrogen retention was 0.68 Gm.

In subjects 1 and 2 the urinary amino acid nitrogen and fecal nitrogen values were within the normal range. The urinary creatinine values were constant ( $\pm 10$  per cent) except for the two days when part of the diet was refused by subject 2. On these two days the creatinine excretion decreased, indicating that a change of diet affected the amount of creatinine excreted.

It is of interest to note that in these two cases when the diet was maintained at the same caloric level of 50 Cal./kilo and approximately 200 mg. of nitrogen per kilogram of body weight, the nitrogen retention

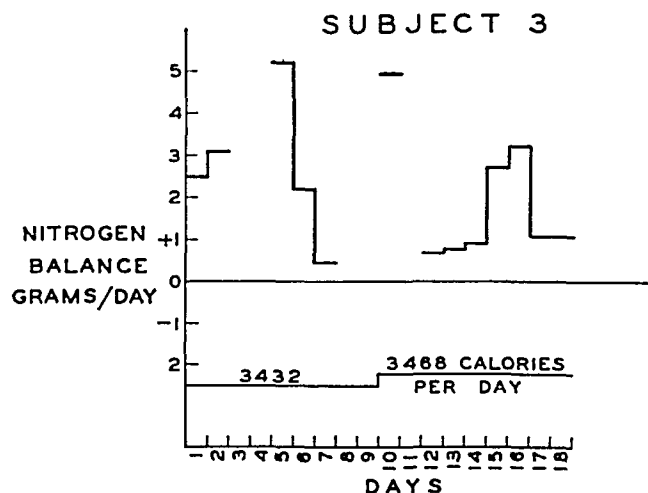


FIG. 3. A nitrogen balance study of an ulcerative colitis patient using enzymatic hydrolyzed casein for the first through the ninth day and acid hydrolyzed casein fortified with one per cent dl-tryptophane for the tenth through the eighteenth day as the sole source of nitrogen.

was approximately the same, 0.61 Gm. and 0.68 Gm. That nitrogen retention is influenced by the total caloric level is indicated by the fact that for subject 1 an increase from 38.5 Cal./kilo to 44.7 Cal./kilo led to an increase in retention of 1.35 Gm./day ( $-2.10$

2. In the case of the two normal adults the average daily nitrogen retention was 0.61 Gm. and 0.68 Gm. when the nitrogen intake was 191 mg. and 211 mg. per kilogram of body weight, respectively. The caloric intake was 50 calories per kilogram for both cases.

3. A patient with ulcerative colitis was maintained in equilibrium by oral administration of Parenamine. The average daily retention of nitrogen was 1.94 Gm. when the daily nitrogen intake contained 273 mg. nitrogen and 58 calories per kilogram of body weight.

4. With adequate caloric intake, a diabetic woman was maintained in positive balance by oral and parenteral administration of Parenamine.

5. These studies emphasize the necessity of an adequate caloric intake in order to maintain a positive nitrogen balance when amino acids are the sole source of nitrogen.

6. No attempt was made to use a basal level of either nitrogen or calories.

## BIBLIOGRAPHY

1. Mueller, A. J., D. Fickas, and W. M. Cox, Jr.: Minimum maintenance requirement of an enzymic casein hydrolysate, *Bull. Johns Hopkins Hosp.*, 72:110, 1942.
2. Altshuler, S. S., M. Sahyun, H. Schneider, and D. Satriano: Clinical use of amino acids for the maintenance of nitrogen equilibrium, *J. A. M. A.*, 121:163, 1943.

3. Elman, R., and D. O. Weiner: Intravenous alimentation, *J. A. M. A.*, 112:796, 1939.
4. Shohl, A. T., A. M. Butler, K. D. Blackfan, and E. MacLachlan: Nitrogen metabolism during the oral and parenteral administration of the amino acids of hydrolyzed casein, *J. Pediat.*, 15:469, 1939.
5. Altshuler, S. S., H. M. Hensel, and M. Sahyun: Maintenance of nitrogen equilibrium of amino acids administered parenterally, *Am. J. M. Sc.*, 200:239, 1940.
6. Curreri, A. R., and O. V. Hibma: Experiences with the parenteral use of amino acids, *Wisconsin M. J.*, June 1944.
7. Abbot, W. E., and R. C. Mellors: Total circulating plasma proteins in surgical patients with dehydration and malnutrition, *J. A. M. A.*, 46:277, 1943.
8. Rose, W. C.: The role of protein in the diet, *Proc. Inst. Med. Chicago*, 15:24, 1944.
9. Kade, C. F.: Unpublished data.
10. Ma, T. S., and G. Zuazuage: Micro-Kjeldahl determination of nitrogen, *Ind. & Eng. Chem., Anal. Ed.*, 14:280, 1942.
11. Folin, O.: On the determination of creatinine and creatine in urine, *J. Biol. Chem.*, 17:469, 1914.
12. Peters, J. H.: The determination of creatinine and creatine in blood and urine with the photoelectric colorimeter, *J. Biol. Chem.*, 146:179, 1942.
13. Albanese, A. A., and V. Irby: Determination of urinary amino nitrogen by the copper method, *J. Biol. Chem.*, 153:583, 1944.
14. Peters, M. P., and D. D. Van Slyke: *Quantitative Clinical Chemistry*, vol. II, Methods, Baltimore, Williams & Wilkins, 1932, p. 77.
15. Jones, J. H., and C. Foster: A salt mixture for use with basal diets either low or high in phosphorus, *J. Nutrition*, 24:245, 1942.

## Some Aspects of Food Rationing

During the war when food was rationed there often arose the question of allowing supplementary food allotments in cases of medical necessity. To aid in judging the validity of these requests the Office of Price Administration at the national and local levels sought the help of the medical profession. Dr. Garland, the chairman of the Massachusetts Committee to Aid the Regional OPA, has recently reported (*New England Journal of Medicine*, Dec. 5, 1946) some of the experiences which his committee encountered.

A defense plant applied for extra meat allowances for several hundred of its employees who worked long hours at the open forge and in the heat treatment of metals. The request was for three pounds of meat per day when the basic ration allowed one and one half pounds of meat, fats and oils per week.

Some applications had to be returned for more specific information as in the case of one patient who was stated to be allergic to all unrationed foods!

"Rations were requested at one time or another for practically all known diseases and in all imaginable quantities. The program, indeed, furnished the ideal example of the universality of headache as a symptom of all diseases—only it was the committee that had the headache. Such requests were made as the following: 14 pounds of meat a week for

a child for normal growth; 7 pounds for the treatment of frequent colds; 4 pounds for the treatment of heartburn; and 2 pounds for the treatment of hoarseness. . . . Other requests included 1 pound of processed foods and 31 of meats and fats a week for a patient with hemiplegia; 40 pounds of processed foods and 12 of meats and fats for another with hypertension; 31 pounds of processed foods and none of meats and fats for a pyelonephritis patient with renal calculi; 9 pounds of processed foods and no extra meats and fats for a patient with duodenal ulcer; and 12½ pounds of meats and fats and none of processed foods for another with the same disease. Too often, no rhyme or reason could be discovered for the types or quantities of foods solicited.

"This particular committee of the Society believed that its functions were to advise and not to police, to make exceptions to any specific policy when a reasonable doubt seemed to exist in any given case and to err on the side of possible indulgence to prevent injustice, and yet to protect the interests of the majority. Our experiences also led us to believe that actually few persons could not have subsisted comfortably on their basic allotments, procured with reasonable intelligence, regardless of the disease."

# WHAT'S YOUR DIAGNOSIS?

A 43-year-old white housewife was admitted to the medical service 8/8/42 with jaundice and weakness.

She had been followed in the outpatient clinic since 1936 because of allergic and psychogenic conditions including allergic rhinitis, asthma, bromide dermatitis, complaints of general nervousness and on two occasions hysterical aphonia. During this time she was always described as poorly nourished, but aside from the allergic manifestations there were never any significant physical findings. Several serologic tests for syphilis were negative. She demonstrated mild skin sensitivity to a wide variety of antigens. A course of desensitization was said to have affected favorably her asthma and hay fever. During the year prior to admission she was under the care of several private physicians and received a variety of medications, the nature of which were not known, except that she was thought to have received several courses of a sulfonamide. It is of interest that at the time of onset of her illness she was on a strict elimination diet. In 1924 her uterus, both tubes and the left ovary were removed apparently because of dysmenorrhea.

Eighteen days before admission to the hospital she rather suddenly developed anorexia, nausea and vom-

iting. Two days later she noticed that her skin was yellow and that her urine was dark in color. She continued to have nausea intermittently and occasionally vomiting, but did not feel sick enough to go to bed. She had no chills and was not aware of feverishness. There was no abdominal pain. The jaundice increased and her stools varied from light brown to clay colored. She was seen in the clinic ten days and again five days before admission. On both occasions her liver was described as one to two fingerbreadths below the costal margin, but not tender, and the icterus index was 45 and 65. She had no fever. Because of increasing jaundice and increasing weakness she was admitted to the hospital.

On physical examination, she was described as undernourished but did not appear acutely ill. She was deeply jaundiced. There were no significant skin lesions. Slight general glandular enlargement was noted. The tip of the tongue was slightly reddened. The heart and lungs were normal. B.P. 110/60. The liver edge was felt two fingerbreadths below the costal margin and was described as smooth and not tender. The spleen was not enlarged. There was no abdominal tenderness and no evidence of ascites.

## LABORATORY DATA

LABORATORY DATA										
Urine					MICROSCOPIC					
HOSP. DAY	SP. GR.	ALB.	SUGAR	BILE						
1	1.018	Neg.	Neg.	Strongly positive	Few WBC; no RBC; many granular casts					
7	1.012	Neg.	4+	Strongly positive	Few WBC; no RBC; no casts					
9	1.010	2+	1+	Strongly positive	Few WBC and granular casts. No RBC					
Blood										
HOSP. DAY	R.B.C.	Hg.	DIFFERENTIAL	ICTERUS INDEX	BLEEDING TIME	SEROLOGY		PROTHROMBIN TIME		
						Wass.	Kahn	Patient	Control	
1	3,900,000	11.5 Gm.	Poly. 79%, Lym. 19%, Mono. 2%	68	1.5 min.	—	+			
2										
3				60					53.8 sec.	15.8 sec.
4				60						
5	2,600,000	12.8 Gm.		60						
6				60						
7				60		—	—	43.7 sec.	16.4 sec.	
8								39.2 sec.	14.9 sec.	
9	5,300,000	15.5 Gm.			3 min.					

Sedimentation rate: 4 mm. per hour.

Fragility test: Increased resistance compared to control.

Van den Bergh: (3rd Hosp. day) immediate direct.

Stool: (3rd Hosp. day) clay colored; bile 0; occult blood 0.

Urobilinogen in 24-hour collection of urine 0.2 mg.

Spinal fluid: Clear; pressure 220 mm. saline; 2 Mono. cells; Pandy—trace.

Glucose tolerance test: Fasting 58; ½ hr. 95; 1 hr. 170; 2 hr. 145; 3 hr. 160; 4 hr. 130 mg. %.

Chest plate: (3rd Hosp. day) Heart is normal. Slight thickened pleura in apices. Small patch of irregular calcification right upper. Increased bronchovascular shadow in both bases. No significant changes in either lung.

Normal findings were present on neurologic examination.

She ran a low-grade fever to 99.4° F. She was treated with intravenous glucose solution. Because of increased prothrombin time, vitamin K was given parenterally. There were no evident bleeding tendencies. On the third hospital day she became restless, excited and then irrational, and it was necessary to sedate her heavily (paraldehyde). She developed

increasing stuporousness and on the seventh day became deeply comatose. There was no stiffness of the neck, no choking of the discs, and no localizing neurologic signs. The conjunctivae were described as injected and edematous. During the last 24 hours signs of pneumonitis appeared at the right base, there was evidence of ascites, her blood pressure dropped and temperature rose to 104° F. She died in respiratory failure on the ninth hospital day.

## BOOK REVIEWS

**MANUAL OF APPLIED NUTRITION.** The Johns Hopkins Hospital, Baltimore, Md., 1946.

This manual, though it contains something of nutrition, would more properly be called a manual of dietetics. It does, however, have a very important practical relation to nutrition and this is perhaps what the authors had in mind when they used the word *applied* in the title. Further evidence of the importance of dietetics to nutrition, which itself has grown greatly in importance in the six years since the first edition, is the co-operation of a committee on nutrition, composed principally of clinicians, in the preparation of the manual.

In addition to a description of the characteristics of the normal diet which fulfills the recommended dietary allowances of the Food and Nutrition Board of the National Research Council, the composition and characteristics of some 32 special diets are given. These include not only special diets of a general nature such as soft and liquid diets with many modifications but diets designed for special diseases and abnormal states such as constipation, diseases of the gall-bladder, diabetes and arthritis. These descriptions usually give the composition in forms of nutrients, calories, protein, fat, carbohydrate and many minerals and vitamins. There is also comment on the adequacy of such diets and pattern meal plans. Some, however, such as the creatin-free and the sprue diets are much less complete. Another section gives routines as followed by various services at the Johns Hopkins Hospital, general rules and suggestions for feeding children, valuable additions on height and weight tables including anthropometric data often not given, physiologic data such as normal values of blood chemistry, routine procedures for various clinical tests and the revised (1945) recommended dietary allowances of

the Food and Nutrition Board, National Research Council. An unusual feature in such a manual are the valuable bibliographic references. As is usual in manuals, references to and descriptions of local administrative procedures are rather extraneous, a bit confusing and should probably be omitted from copies designed for general sale. There is also occasional reference to commercial products. The manual is recommended as a source of very much useful dietetic information which is even more important in view of the present position of nutrition in medical practice.

J. B. Y.

**THE CHALLENGE OF POLIO.** By Roland H. Berg. 208 pp. New York, Dial Press, 1946. \$2.50.

This review of the development of knowledge concerning acute anterior poliomyelitis is an interestingly written and informative treatise designed for the lay reader but also of general interest to physicians. It highlights the role of the National Foundation for Poliomyelitis in the development of new ideas and will undoubtedly serve as propaganda source for their campaign.

As a whole the material is factually correct and reasonably interpreted though at times the roles of certain individual investigators are emphasized while others have been neglected. Toomey's contributions to the role of the gastro-intestinal tract in relationship to pathogenesis of the disease are not mentioned.

The implication that early medical treatment will greatly affect the course of the disease is perhaps as unfortunate as it is untrue. In fact, one may say that he unjustifiably stresses the values of treatment.

His treatment of the Kenney controversy seems reasonably objective but again over-emphasizes the results to be expected from treatment.

J. C. PETERSON, M.D.

# The Diagnosis and Management of Acute Arthritis\*

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*Acute arthritis is commonly met in the practice of medicine. At times the etiologic diagnosis is not clear and may be puzzling to the physician. The author of this paper clearly describes the lines of thought which should be followed in such cases.*

While the majority of cases of joint disease have an insidious and gradual onset, the patient whose involvement develops in a few hours or a few days is not uncommon, and often presents a more puzzling problem with respect to differential diagnosis and a more urgent demand for prompt relief of symptoms. Accurate diagnosis is especially important since specific methods of treatment are available for some forms of acute arthritis and serious permanent impairment of joint function can be avoided by the prompt institution of proper management. Even in those forms where specific treatment is not available, the prognosis depends to a very large extent on the underlying etiology.

The correct diagnosis can usually be made clinically with a minimum of special laboratory procedures if the various possibilities of causation are kept in mind. Erroneous diagnoses are more frequently due to failure to consider all the diseases which present acute joint manifestations than to any other single factor. These diseases are most frequently acute rheumatic fever, rheumatoid arthritis with acute onset, gout, gonorrheal arthritis, other forms of septic arthritis, Reiter's disease and traumatic arthritis. Occasionally nonarticular rheumatism, especially bursitis, may have a sudden onset, and less frequently acute joint manifestations may appear in the course of other diseases, such as bacillary dysentery, ulcerative colitis, syphilis and disseminated vascular disease. A complete history and physical examination, plus a blood count, urinalysis and sedimentation rate determination will usually indicate in which classification the particular patient falls. At times, additional laboratory tests may be necessary to establish the diagnosis.

The age, sex, and occupation of the patient will often give a strong presumptive lead to the nature of the etiology. In the history, there is need for detailed questioning regarding the location of original joint involvement, the sequence in which others were subsequently affected, the duration and character of symptoms at each site, the occurrence of constitutional symptoms such as chills and fever. Especially important is the history of illnesses preceding the joint manifestations by a few days to a few weeks, or of possible precipitating factors, including medication, trauma and surgical procedures. Attention to the characteristics, duration and sequelae of any previous joint difficulty resembling the current attack, may be particularly helpful. The occurrence of similar attacks in other members of the family should not be overlooked.

The physical examination must be complete and not just an inspection of the involved joints. These must be checked carefully to see if the objective findings are proportional to the patient's complaints and to make sure that muscle or bone pain, which have a much different significance, are not being interpreted by the patient as joint pain. In addition, the asymptomatic joints, which sometimes includes the spine, should be checked as well. Particularly important is a careful examination of the heart. The presence of infection in the upper respiratory tract and in the genito-urinary tract must be searched for. Cutaneous lesions which may be helpful in establishing the diagnosis are frequently overlooked. In the laboratory the white blood cell count, including a differential count, and the sedimentation rate will be helpful in differentiating inflammatory joint disease from those due to trauma or mechanical causes.

## ACUTE RHEUMATIC FEVER

**Clinical Features and Course.** The *original* attack of rheumatic fever occurs before the age of 15 in 90 per cent of the patients. The episodes are usually preceded by a sore throat or tonsillitis, and characteristically have a latent period of from 10 to 14 days intervening between the throat infection and the on-

\* From the Rackham Arthritis Research Unit and the Department of Internal Medicine, the Medical School, University of Michigan. The Rackham Arthritis Research Unit is supported by a grant from the Horace H. Rackham School of Graduate Studies.



set of joint manifestations. Fever may range as high as 104° F., but more often is moderate, between 100° and 102° F. The outstanding characteristic of the joint involvement is its migratory nature with a tendency for the inflammatory process to pass rapidly from joint to joint, often subsiding entirely in one joint as another is involved. Larger joints, the knees, ankles, shoulders and wrists, are usually the earliest and most frequently involved, but any joint may be affected. Symmetrical involvement is frequent, and the inflammation may appear and subside several times in the same joint. Swelling, increased heat, redness, tenderness and marked pain on motion of the affected joints are present in various degrees. But permanent joint damage never occurs in rheumatic fever. X-ray examination rarely shows more than soft-tissue swelling.

The fever is usually accompanied by profuse sweating. Tachycardia, often out of proportion to the fever, is prominent. With the use of salicylates or amidopyrine, the temperature usually falls in a few days and the joint manifestations are suppressed. In untreated cases the fever and arthritis last from four to six weeks. There is a marked tendency to recurrence, either in a few months or almost immediately in the "polycyclic" attacks. Cardiac damage is nearly always present in recurrent attacks, and may be manifest by murmurs, prolongation of the auricoventricular conduction time, or pericardial effusion. Involvement of lungs and pleura is not infrequent.

Over 10 per cent of patients with rheumatic fever present cutaneous erythemas which appear and disappear irregularly with wide fluctuations in intensity. These include erythema nodosum, erythema multiforme, small purpuric, papular or urticarial lesions and erythema annulare rheumaticum. In addition, about 20 per cent will show subcutaneous nodules varying from pin-head to lima-bean size which are firm, nontender and attached to tendons or fibrous tissue rather than to the skin. They occur most frequently adjacent to but not over joints. Since similar nodules are seen in about the same percentage of patients with rheumatoid arthritis, their presence is not diagnostic.

The most consistent laboratory finding in rheumatic fever is an increased rapidity of sedimentation of the erythrocytes, and in general this constitutes the best index of persisting infection. In the acute stages leukocytosis with a shift to the left in the granulocyte series is often present; this usually returns to normal before the sedimentation rate. The electrocardiogram may detect myocardial disturbance before there is clinical evidence of cardiac involvement. Joint effusions rarely are extensive enough to suggest joint aspiration, and examination of the joint fluid is of

little help in establishing the diagnosis. Such joint fluids as have been studied in rheumatic fever show cell counts totalling from 3,000 to 10,000 per cubic millimeter with a preponderance of polymorphonuclear cells. The mucin is apparently normal in quality and sugar content is not decreased.

It should be noted that many cases of rheumatic fever, especially in children, have an insidious onset. In these patients the constitutional symptoms predominate and joint complaints are variable or at times absent.

**Diagnosis.** No single clinical finding or laboratory test is pathognomonic of rheumatic fever. The outstanding features are the migratory nature of the arthritis, the frequency of cardiac involvement, the effective suppression of fever and inflammatory joint manifestations by salicylates or amidopyrine. Laboratory tests are more helpful in following the activity of the rheumatic process than in differentiating it from other febrile diseases. The absence of residual joint damage and the frequency of permanent cardiac damage are the major factors in deciding whether previous attacks of acute joint disease can be attributed to rheumatic fever. At times the diagnosis can only be presumptive until response to therapy and clinical course of the disease have been observed.

**Treatment.** The most important item in treatment is bed rest until there is satisfactory evidence that the activity of the rheumatic process has subsided. Generally bed rest should continue until the sedimentation rate has returned to normal.

The beneficial effect of salicylates on the joint manifestations and fever in this disease is established. These are usually given in divided doses totalling 4 to 8 Gm. daily, the dosage being increased until the desired therapeutic effect is obtained. In 1943, work by Coburn<sup>1</sup> suggested that larger doses of salicylates (10 to 20 Gm. per day), and use of the intravenous route of administration, may prevent the development of cardiac complications. Subsequent observations<sup>2-4</sup> have indicated that cardiac involvement may appear in spite of maintenance of plasma salicylates above the recommended level of 35 mg. per 100 cc., that the intravenous administration is not often necessary to attain the desired blood levels, and that serious salicylate intoxication can develop during such treatment. In our experience, such serious toxic effects have occurred almost entirely in patients who did not receive sodium bicarbonate with the salicylates and were most serious in patients who already had cardiac involvement, in whom treatment of the salicylate intoxication may precipitate congestive cardiac failure. It appears that large doses of salicylates can be used more safely and as effectively if the program suggested

by Manchester<sup>5</sup> is followed. "More severely infected patients with temperatures of over 102° F. but without cardiac failure, receive intravenous therapy of 10 Gm. daily in a liter of Ringer's lactate solution for four to seven days, followed by oral therapy. A period of six hours is required for each injection. Patients with cardiac failure are treated with 4 to 6 Gm. of amidopyrine daily until failure has subsided and then switched to oral salicylates. Other patients receive oral salicylates from the beginning in quantities of 10 Gm. daily in patients weighing less than 125 pounds (57 Kg.) and 12 Gm. daily in those exceeding 125 pounds. Eight to 10 Gm. of sodium bicarbonate is given daily in conjunction with oral therapy. Refractory cases are promptly shifted to intravenous medication until objective acute manifestations are completely relieved. Salicylate therapy is continued until the erythrocyte sedimentation rate has remained normal for two weeks."

When the sedimentation rate has returned to normal or nearly to normal, in the presence of normal pulse, temperature and white count, and in the absence of clinical activity of the rheumatic process, the patient should be observed for an additional one to two weeks at bed rest after the antirheumatic drugs have been discontinued. If the clinical condition and laboratory tests remain satisfactory, graded and gradual resumption of activity is permitted. Maintenance of general health, with particular attention to adequate rest and an adequate diet is urged to prevent recurrences. The use of sulfanilamide or sulfadiazine in doses of 0.5 Gm. to 1.2 Gm. daily during the winter and spring months has materially reduced the frequency of recurrences. These drugs, as well as penicillin, have no effect on the active rheumatic process.

### RHEUMATOID ARTHRITIS

**Clinical Features and Course.** Ten to fifteen per cent of patients with rheumatoid arthritis have an acute onset with some degree of constitutional reaction and fever. These may closely resemble acute rheumatic fever or gonorrheal arthritis, particularly at the onset. The age incidence of rheumatoid arthritis places the onset above the age of 15 years in 90 per cent of the patients. The migratory nature of the joint involvement so characteristic of rheumatic fever is not often seen in rheumatoid arthritis. While the process may progress from one joint to another there is usually persistent evidence of synovial inflammation for weeks or months in some of the previously affected articulations. While the smaller joints, particularly the proximal interphalangeal joints of the fingers and the metatarsal-phalangeal

joints of the toes, are more often affected in rheumatoid arthritis, the location of the involved joints is less helpful than the character and persistence of involvement. Swelling, heat, pain on motion, and effusion are moderate to severe. Permanent joint damage, so rare in rheumatic fever, is the rule in rheumatoid arthritis. Persistence of active synovitis, progressive limitation of motion or residual joint deformity after the acute inflammatory phase has subsided are suggestive of the latter condition. While the x-rays of the joints may show only effusion and soft-tissue swelling early in the disease, regional osteoporosis appears fairly early, and later loss of joint space and changes in subarticular bone give evidence of irreversible damage to cartilage.

While low-grade fever and only slight leukocytosis are more common in rheumatoid arthritis, persistent temperature elevations to 103° or 104° F. with white counts of 15,000 or more have been observed without any other explanation. Tachycardia is common and is proportional to the fever. Cardiac damage is rare, at least insofar as evidence of it can be detected by clinical examination and electrocardiography.

The response of both fever and joint symptoms to salicylates in rheumatoid arthritis is not as marked as in rheumatic fever. The temperature is usually lowered, at times to normal, and the joint pains alleviated, but rarely is there complete and prompt suppression of the inflammatory synovial process.

Laboratory findings include frequent leukocytosis and almost constantly an elevated sedimentation rate. Varying degrees of anemia are common. The joint fluid may show much variation in cell count with a preponderance of counts above 3,000–5,000 per cubic millimeter, of which 50 to 90 per cent or polymorphonuclear. Early in the disease mucin quality and sugar content are near normal, but within a few months of onset these may show decreases.

**Diagnosis.** Again there are no pathognomonic signs or laboratory tests. The clinical course, especially the character and chronicity of the joint involvement and the incomplete response to salicylates, serve best to differentiate it from rheumatic fever. It is differentiated from gout, septic arthritis, etc., by the absence of certain clinical and laboratory features to be discussed later. There are some cases, particularly in children, in which the condition cannot be differentiated from rheumatic fever even after several weeks of observation. Common sense dictates that such patients should be treated systemically for rheumatic fever, with local care to the persistently involved joints as is used in rheumatoid arthritis.

**Treatment.** Rest in bed should be insisted upon in the acute febrile stage of the disease with acutely in-

flamed joints. If weight-bearing joints are involved it should be continued until all evidence of active inflammation has subsided. Salicylates in dosage totaling 3 to 6 Gm. per day are helpful in reducing pain and permitting adequate rest. Massive salicylate therapy as recommended by Coburn in rheumatic fever has been used by us in acute rheumatoid arthritis and appears to offer no better immediate or long range results than lower levels of dosage as necessary to relieve symptoms. Acutely painful joints can be relieved by immobilization by splints in a position of physiologic rest, or if ankylosis appears imminent, in a position of optimum function for the particular joint.

Special care to the affected joints is indicated to prevent or minimize deformity. Even in the acute stage, splints should be removed each day and the joint moved once or twice through a full range of painless motion. As the inflammation becomes sub-acute or chronic, the use of heat and of massage to the muscles around the joint is introduced. As soon as muscle spasm subsides, active exercise can be added to these measures. These physical therapy measures must be adjusted to the general condition of the patient as well as the local joint involvement, and should not be carried to the point of persisting pain or fatigue.

Other general measures, in addition to rest, can be put into effect as the patient's condition improves. These include restoration or maintenance of adequate nutrition, with emphasis on protein and vitamin intake, correction of anemia, removal of definite focal infections, and attention to all the factors which bear on the individual's general health. The patient will usually do well on such a program, and special measures of treatment such as gold salts, foreign protein therapy, etc., are not necessary unless the disease is observed to pass into the stage of chronic progressive activity.

## GOUT

**Clinical Features and Course.** This disease occurs almost exclusively (95 per cent) in males and seldom has its onset before the age of 35 years. It is characterized by recurrent attacks of severe pain, redness and swelling in one or more joints which persist for a few days to a few weeks and subside completely, leaving no residual until after many such recurrent acute episodes. The onset frequently occurs at night and severe incapacitating pain, with redness, heat, swelling and exquisite tenderness develop in the next 6 to 24 hours. The initial attack is usually mono-articular and affects the metatarsal phalangeal joint of the great toe in about 70 per cent of the patients.

Later attacks are frequently migratory or may involve two or more joints simultaneously. The gouty patient is often but not universally overweight and will often give a history of similar episodes in other male members of the family. Attacks seem particularly prone to develop after drinking bouts, after minimal trauma to the joint affected, during unusual activity such as hunting and fishing trips, postoperatively, and after the use of liver extract or salyrgan in treatment of other diseases. Acute arthritis in men developing a few days after major or minor surgery should be regarded as gout unless it can be ruled out.

Not only is the local joint inflammation often so severe as to suggest a septic process, but fever and leukocytosis are often present, at times to a degree compatible with septicemia. Surgical treatment or chemotherapy may be undertaken under the impression that one is dealing with a septic joint or cellulitis. The sedimentation rate is elevated during acute attacks, but falls to normal rapidly after the attack subsides. Several typical features are illustrated by the following case:

**CASE 1.** A 46-year-old male accountant was admitted on the Bone and Joint Surgery Service with a painful, red, swollen right knee. The process had begun ten days previously in the right great toe with pain and swelling which developed during the night and was sufficiently severe within 24 hours to prevent weight-bearing or wearing of a shoe. Three days later the right ankle had been similarly involved. With elevation of the foot, rest, and ice bags the inflammation in these joints was subsiding when, two days before admission, the right knee began to swell and become painful.

The first episode of joint pain had occurred ten years before with swelling, redness, and tenderness of the left ankle having appeared after playing handball and subsided in a week without medical attention. Eight years before, the left great toe had become greatly swollen, red and painful following trauma from dropping a weight on it. This subsided in about a week. Since then, on an average of once or twice a year, he had experienced similar attacks in the left great toe and both ankles, usually coming on a night, lasting from three to ten days; the affected joints were somewhat stiff for a week following the attack, thereafter entirely normal. Three years before, the right knees had been involved in an attack which had started in both ankles and incapacitated him for over six weeks. Aspiration of the knee had been done with reported negative cultures, and the knee placed in a cast for two weeks. At no time had the patient received a diagnosis other than "synovitis." Family history was negative, but the patient had no knowledge of the health histories of his male relatives.

On admission temperature was 102° F., pulse 100, B.P. 124/80. The patient was moderately overweight but without any abnormal findings except for the joint findings. The right knee was greatly swollen, hot and fluctuant, held in 15° of flexion by muscle spasm and any attempt at motion was excruciatingly painful. There were two fiery red patches of erythema in the skin over the knee, about 1½

inches in diameter. The right ankle was swollen and there was pain on motion. There was redness around the medial malleolus and the base of the right great toe. Careful search revealed no tophi.

Blood studies were normal aside from a white blood cell count of 12,650/cu. mm., with 68 per cent polymorphonuclears. Urinalysis and Kahn test were negative. Serum urate concentration was 6.8 mg. per 100 cc. X-ray examination revealed irregularity of the margin of the right patella and of the tarsal bones, attributed to developmental anomalies. Localized areas of rarefaction in the heads of both metatarsals were overlooked at the time of the first reading, later reported as signs of relatively early gout; this is in contrast with the clinical story.

The patient was given colchicine 0.5 mg. every hour for 16 doses on the third day of hospitalization. There was some diminution of pain and swelling in the right knee and the involvement of the right ankle and toe subsided completely, coincident with a brisk diarrhea. The following day, however, the left knee became acutely involved, so the same dosage of colchicine was repeated on the fifth hospital day with dramatic relief of pain and swelling in both knees. Temperature had reached 100° F. or higher daily until the sixth hospital day; thereafter it remained normal. Some effusion persisted in the right knee for the following week, after which all joints were objectively normal.

During subsequent observation, weight reduction of 20 lb., a low purine diet, the use of sodium salicylate in doses of 4 Gm. daily for three days of each week, and the interval use of colchicine in doses of 0.5 mg. twice daily have had no persistent effect on the blood urate level. Two later acute attacks of gout have been controlled with intensive colchicine treatment as described above, with only one or two days incapacitation from each attack.

Tophi, the subcutaneous deposits of urates seen particularly in the cartilage of the ears, are occasionally observed early in the disease but usually do not appear until after several years of recurrent acute attacks. Their presence is not necessary for a presumptive diagnosis of gout. The course of the disease is extremely variable as regards frequency of recurrence of acute attacks and the occurrence and severity of permanent joint damage in the later stages. Some individuals will have only three or four acute attacks during their lifetime, others may have progressive increase in frequency to several attacks a year and develop incapacitating deformities due to urate depositions in and around joints.

**Diagnosis.** The diagnosis rests on (a) the clinical course of the disease, with emphasis on the age and sex of the patient, (b) the demonstration of an increase in concentration of urates in the blood and (c) the therapeutic response to colchicine properly administered. If tophi are present, the diagnosis can be clinched by scraping the subcutaneous nodule with a Hagedorn needle or knife blade, suspending the chalky material obtained in a few drops of water or saline and demonstrating the needle-like crystals of sodium monourate by direct examination under the

low power of the microscope. A subcutaneous nodule is not a tophus until this has been done.

In our experience, hyperuricemia can be demonstrated in all patients with gout, even in the initial attack. Some of the discrepancies noted by others in this respect may be due to the several technics used in blood-urate determinations, each of which gives a somewhat different range of normal values, and to the fact that salicylates, often self-administered or prescribed prior to the biochemical determination, can cause a transient depression of the blood concentration and give false normal values. The use of serum rather than whole blood eliminates some of the factors interfering with accurate determination and gives a sharper distinction between the upper limit of normal range and definitely elevated levels. Using the method of Folin<sup>6</sup> on serum, values above 5 mg. per cent are rarely seen in nongouty arthritics, values of 6 mg. per cent or greater have been obtained in nearly all gouty patients.

We have also found that the response to colchicine, given in the manner detailed below, is so consistent in gouty patients as to have diagnostic value. Such therapeutic trial is justified in patients presenting a typical clinical picture where confirmation by biochemical methods is not available. Failures may occur with insufficient dosage or use of preparations of varying potency, such as wine or tincture of colchicine.

The x-ray appearance of affected joints may suggest gout, but cannot be depended on for the diagnosis. In early attacks, only soft-tissue swelling may be present; the punched out juxta-articular areas of decreased bone density seen in later stages is not pathognomonic of gout, as it may be closely simulated in some cases of rheumatoid arthritis.

**Treatment.** For acute attacks, colchicine is prescribed in pills or capsules of 0.5 to 0.65 mg. (gr. 1/120 or gr. 1/100), with directions to take one every hour until (a) pain is relieved, or (b) diarrhea occurs, or (c) 20 doses have been taken. After a total dose which varies with the individual from 3 to 10 mg., there will be a marked reduction in joint pain and inflammation, usually coincident with loose bowel movements. At this point colchicine is discontinued and paregoric taken in doses of 4 cc. after each loose stool. The patient is advised to keep these medications with him on trips so he will have them available at all times; it is usually convenient to make them a permanent addition to his shaving kit. With experience the gouty patient can usually recognize an attack in its early stages or even prodromal symptoms. Under these circumstances three or four doses of colchicine at hourly intervals may abort the attack. Special attention to the affected joints may be neces-

sary, primarily with respect to protection, nonweight bearing and elevation. Resumption of weight bearing should be gradual and begun after inflammatory changes and pain have subsided.

The treatment of the hyperuricemia and of the advanced stage of chronic gouty arthritis is much less satisfactory. A diet avoiding foods rich in purine and usually low in calories to permit weight reduction is indicated. Moderation in use of alcohol is advisable, and if there is any impairment of liver function alcohol should be eliminated. Salicylates in doses of from 3 to 4 Gm. per day will increase the urinary excretion of urates and lower the blood concentration for a variable length of time. Such doses can be used for three or four days each week, combined with equal amounts of sodium bicarbonate to ensure an alkaline urine to minimize the dangers of urate calculi. Since both urate diuresis and control of pain can be obtained with safer medications, the use of cinchophen is not recommended. The value of daily small doses of colchicine (0.5 mg. two or three times daily) in intervals between acute attacks is debatable. Undoubtedly the variability of the course of the disease is an important factor in the difficulties of evaluating the "interval treatment" in this disease.

### GONORRHEAL ARTHRITIS

**Clinical Features and Course.** Gonorrhea can be accompanied by joint disease ranging from simple arthralgia without objective findings, through sterile joint effusions with pain and swelling, to severe purulent arthritis with rapid destruction of the articular cartilage. The joint symptoms usually follow the onset of genital gonorrhea by 10 to 20 days, but may occur several weeks later. The involvement is polyarticular and migratory at the onset in the great majority of cases, but after several days may settle down as a stubborn involvement of one or a few joints. Asymmetric involvement of larger joints is the rule, with the knee, ankle, wrist and metacarpal phalangeal joints most frequently affected. Actual observations do not support the well perpetuated misconceptions of this disease as usually being entirely a mono-articular arthritis with an unusual affinity for the sternoclavicular, the temporomandibular joints, or the spine. Preceding or accompanying the joint involvement there is often a chill and usually a fever, which may be slight or septic in type. A polymorphonuclear leukocytosis is nearly always present. Iritis and tenosynovitis occur much more commonly in this condition than in other forms of rheumatic disease.

Before the days of the sulfonamide drugs and penicillin, gonorrheal arthritis was seen much more frequently in males. In the past three years, the dis-

ease has been seen much less frequently, has often been mistaken for rheumatic fever, and most of the cases have been in females. This is probably due to the greater difficulty in making the diagnosis of genital gonorrhea in the female, with consequent delay in effective treatment.

**CASE 2.** A 21-year-old married woman was admitted on December 11, 1945 with complaints of a painful swollen right ankle. Four days before, she awakened with a painful, tender left knee; there was also slight pain in the right elbow. The following day the right ankle became painful, then progressively swollen, red, and painful to walk on. There was associated disappearance of pain in the previously involved joints. Exposure to venereal disease and vaginal discharge were denied. There was a past history of pain and swelling of the ankles, elbows, and wrists at the age of 13, lasting two weeks.

Temperature on admission was 100.2° F., pulse 124. The patient was flushed and perspiring freely. The heart was normal in size and position, regular without murmurs. The right ankle was red, warm, tender, swollen but without free fluid, and painful on motion. Other joints, and the remainder of the physical examination, were normal. The white blood count was 16,500 per cu. mm. with 71 per cent polymorphonuclears, sedimentation rate 0.9 mm. per minute, blood Kahn test negative. Electrocardiogram was within normal limits. Roentgen examination showed soft tissue prominence and minimal osteoporosis of the right ankle.

She was placed on bed rest and given 6.5 Gm. of sodium salicylate daily in divided doses. The fever, which reached 100° F. daily during the first six days, remained normal thereafter. The ankles showed no significant change during three weeks on this regimen.

Positive complement-fixation tests for gonorrhea were obtained on the blood on 12/15/45 and 12/24/45. On 12/31/45 urethral smear showed Gram-negative intracellular diplococci, and cultures from the cervix and urethra taken on the same date were positive for *N. gonorrhea*. The following day she was started on penicillin, 15,000 units intramuscularly every three hours. Within three days there was definite improvement in the ankle but the process did not completely subside until the ninth day of treatment.

**Diagnosis.** This rests on the association of a demonstrable gonorrheal infection in the genital tract with an arthritis with the clinical characteristics outlined above. The diagnosis is confirmed by laboratory studies, the most definite of which is the recovery of the causative organism in the joint fluid. This, however, can be accomplished, even by cultural methods, in only 25 per cent of the cases. The cytologic characteristics of the joint fluid may be helpful, although not pathognomonic. The cell count is usually much higher than in the other conditions discussed, from 15,000 to 30,000 per cu. mm., with 90 to 100 per cent polynuclear cells. Mucin quality is poor and sugar content lowered.

Properly performed, the complement-fixation test is positive in 80 per cent or more of patients with this

disease. It may not become positive during the first two weeks so a negative test early in the disease does not rule out Niesserian etiology. Repetition in seven or ten days may give a positive reaction. There is no advantage in performing the test on joint fluid, as the reaction becomes positive in the blood before it does in the joint fluid. The test remains positive from a few weeks to two years after joint manifestations have subsided. Since persistently positive reactions are obtained in only 2 per cent of patients with rheumatoid arthritis, it may be of considerable aid.

While the x-ray appearance of localized joint destruction is fairly characteristic in its advanced stages, the roentgen appearance in the early stages when effective therapy can prevent permanent joint damage is nonspecific.

**Treatment.** Penicillin is undoubtedly the treatment of choice, with doses of 15,000 to 20,000 units every three hours by intramuscular injection usually sufficient. The response of the joints is not as dramatic as might be expected from the experience with this agent in treating genital gonorrhea, and in general more prolonged treatment—10 to 14 days—is needed before the arthritic manifestations subside. In severe suppurative joints intra-articular injection of penicillin in doses of 10,000–20,000 units has been used. The condition also can be effectively treated with sulfonamide drugs. In resistant cases, these may be combined with penicillin, or artificial fever therapy may be added.

These patients will usually recover normal activity more rapidly if physical therapy or weight bearing are not resumed until all evidence of inflammation and joint irritability have subsided. Immobilization may be helpful in controlling pain, and there seems to be little danger of ankylosis after the acute inflammatory process is controlled.

### REITER'S DISEASE

Although this condition was first described in this country only in 1942,<sup>7</sup> the number of recently reported cases<sup>8,9</sup> and our own experience make us feel that it is not a rare disease. It is apparently restricted to young adult males and is characterized by urethritis, conjunctivitis and joint involvement. The purulent urethritis usually ushers in the triad of manifestations, being followed in a few days to a week with a transient conjunctivitis of the catarrhal type. Two to three weeks later joint pain and swelling appear, without following any as yet well defined characteristic pattern. No specific causative organisms have been isolated consistently from the genitourinary, ocular or joint exudates. The urethritis

and conjunctivitis subside spontaneously in a week or two, but the joint involvement may persist for weeks or months with clinical features closely resembling rheumatoid arthritis. It is stated that the findings of the joint fluid and synovial biopsy are indistinguishable from those in rheumatoid arthritis. The diagnosis is made by exclusion of gonococcal etiology, by failure to find this organism in urethral discharge by smear and culture, and by persistently negative complement-fixation reactions.

Undoubtedly many of these cases have been labelled gonorrheal arthritis, when bacteriologic or immunologic proof of the latter diagnosis was not sought or could not be obtained. The differentiation is of practical importance since (a) Reiter's disease does not respond to penicillin or sulfonamide therapy, and (b) the prognosis for ultimate recovery of joint function in this disease is good, although the course may be prolonged and joint involvement may recur in as high as 25 per cent.

### SUMMARY

Accurate diagnosis of acute joint diseases can usually be accomplished by attention to details of the history and physical examination; at times certain laboratory tests may be necessary to confirm the diagnosis. Immediate management and ultimate prognosis with respect to joint function are dependent on the underlying disease producing the joint manifestations. The clinical features, diagnostic criteria, and fundamentals of treatment of the more common acute inflammatory forms of arthritis are discussed.

### BIBLIOGRAPHY

1. Coburn, A. F.: Salicylate therapy in rheumatic fever; rational technique, *Bull. Johns Hopkins Hosp.*, 73: 435, 1943.
2. Wegria, R., and K. Smull: Salicylate therapy in acute rheumatic fever, *J. A. M. A.*, 129:485 (Oct. 13) 1945.
3. Murphy, G. E.: Objective clinical histologic study of effects of salicylate on rheumatic lesions, those of joints and tendon sheaths in particular, *Bull. Johns Hopkins Hosp.*, 77:1 (July) 1945.
4. Jager, J. V., and R. Alway: The treatment of acute rheumatic fever with large doses of sodium salicylate, *Am. J. Med. Sci.*, 211:346 (March) 1946.
5. Manchester, R. C.: Rheumatic fever in Naval enlisted personnel, *J. A. M. A.*, 131:209 (May 18) 1946.
6. Folin, O.: Determination of uric acid, *J. Biol. Chem.*, 101:111, 1933.
7. Bauer, W., and E. P. Engleman: A syndrome of unknown etiology characterized by urethritis, conjunctivitis and arthritis (so-called Reiter's disease), *Trans. Assoc. Amer. Phys.*, 57:307, 1942.
8. Rosenblum, H. H.: So-called Reiter's disease; triad of acute arthritis, conjunctivitis and urethritis, *U. S. Navy Med. Bull.*, 44:375, 1945.
9. Feiring, W.: Reiter's disease with prolonged auriculo-ventricular conduction, *Ann. Int. Med.*, 25:498, 1946.

# Myocarditis in Infectious Diseases\*

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*In the past decade or more the diagnosis of myocarditis has fallen into disrepute because of the emphasis upon cardiac physiology and abnormalities of function. The author recalls for us that myocarditis does occur and must be reckoned with in clinical practice.*

One of the problems facing medicine today is that of ascertaining the effect of various diseases upon the heart muscle. Possibly as a reaction to the practice of the not so remote time when the diagnosis of chronic myocarditis appeared on the death certificates of most elderly persons, the current generation of physicians have been trained to consider myocarditis a rare disease. Speaking of diseases other than rheumatic fever, diphtheria, or scarlet fever, White<sup>1</sup> approved in large part the abandonment of this diagnosis. Christian,<sup>2</sup> while emphasizing the frequent occurrence of circulatory disturbances in acute infectious disease, intimated that they usually had a functional basis but that "exceptionally there occurs acute inflammatory change in the myocardium." Sir Thomas Lewis<sup>3</sup> also stressed the physiologic disturbance and minimized the possibility of an anatomic lesion of the heart muscle. As a working basis, these teachings have proved their value and have led to the recognition of the predominant role of vascular disease in what was formerly loosely termed myocarditis;<sup>4</sup> to continue to assert them, however, would hamper further progress.

Electrocardiographic disturbances of a transient nature have been recognized in a variety of acute infectious processes.<sup>5-12</sup> Because of the dearth of demonstrable anatomic changes they have usually been regarded as evidence of functional disorders. To cite a few instances, electrocardiographic abnormalities have been reported in a significant percentage of cases of typhoid fever, typhus, gonorrheal arthritis, pulmonary tuberculosis, malaria, rheumatoid arthritis, pneumonia, influenza, parotitis, infectious mononucleosis. Rantz, Spink, and Boisvert,<sup>13</sup> investigating acute streptococcal throat infections during the war, found abnormal electrocardiograms in 31 of 185

patients. Candel and Wheelock<sup>12</sup> reported an instance of severe myocarditis at autopsy and inferred that similar cardiac changes were responsible for the electrocardiographic disturbances they had observed following a number of other acute infections. Nevertheless, to explain why a substantial pathologic background is absent, we must infer that if postinfectious myocarditis is the basis for the reported abnormalities (1) it is not a particularly fatal disease, or (2) insufficient material has been observed pathologically to eliminate the possibility of chance or coincidence from any correlation made, or (3) many cases of myocarditis have been overlooked because the examination of the heart was inadequate.

During the recent war 1,402 cases of myocarditis accumulated at the Army Institute of Pathology, a figure which seems startlingly large in view of the general impression that the condition is rare.<sup>14</sup> It is not surprising, considering that impression, that clinical recognition of the myocarditis was infrequent, even though the cardiac complication in the majority of cases was instrumental in causing death. More significantly the clinical records clearly set forth the manifestations of cardiac embarrassment. That they were ignored testifies to the low index of suspicion fostered by recent authoritative teaching.

*Syphilis* is the one disease in which there does not appear to be a general reluctance to consider myocarditis. Warthin's assertion that myocarditis is frequent in this disease<sup>15</sup> has acquired a peculiarly tenacious hold, with the result that physicians are prone to make a diagnosis of syphilis in the occasional case of myocarditis that comes to their attention, probably because no other explanation occurs to them.<sup>16</sup> This continues in spite of the singular failure to duplicate Warthin's findings. Instead there is an abundance of irrefutable evidence that, except for a rare gumma, myocardial changes in cardiovascular syphilis can be attributed almost entirely to vascular changes: narrowing of the coronary ostia or arteriosclerosis.<sup>17-20</sup> These observations were confirmed in a review of the material available at the Army Institute of Pathology. Among 66 cases of cardiovascular syphilis, the myocardial changes consisted of focal fibroses, with a variable degree of perivascular round cell infiltration in

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FIG. 1. Focal area of acute degeneration within the heart muscle of a 24-year-old white male with acute tonsillitis. Hospitalized on the second day, he seemed to be responding satisfactorily to treatment, when he died suddenly on the fourth day. AIP Neg. 95853,  $\times 275$ .

33, acute or subacute infarcts in 6 and gumma in 2. Of the 39 hearts with myocardial alterations other than gumma, there was narrowing of the coronary ostia in 21, frequently combined with coronary arteriosclerosis; and moderate to extensive coronary sclerosis in 15 additional. In only three instances was there myocardial involvement associated with less than a moderate degree of coronary disease. The condition of the heart in these could be easily explained as the result of a complicating nonsyphilitic infection; there were two instances of bacteremia (pneumonic in one and subacute bacterial endocarditis in a second) and one of severe and extensive pneumonia.

The frequency of myocarditis in the common acute infections of the upper respiratory tract is not generally appreciated. Scherf<sup>21</sup> estimated that this complication occurred in 10 to 15 per cent of all cases of acute tonsillitis. Rantz, Spink, and Boisvert, previously cited,<sup>18</sup> reported that clinical evidence of myocarditis subsequently appeared in 22 of 185 patients with acute hemolytic streptococcal sore throats. Nine others had typical rheumatic arthritis with carditis. Until recently there was essentially no information

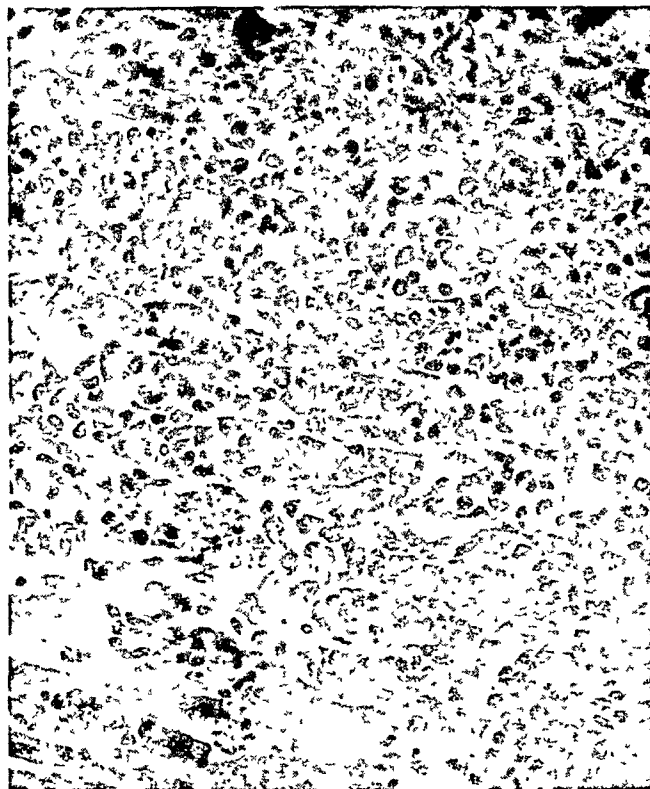


FIG. 2. Severe diffuse myocarditis in a 24-year-old white male with acute nasopharyngitis. A considerable portion of the myocardium has been destroyed. The patient had been admitted to the hospital with recurrence of nasopharyngitis 22 days after a previous attack. Symptoms included chest pain, and temperature-pulse disproportion (T. 101.8° F., P. 78). AIP Neg. 95857,  $\times 310$ .

available concerning the pathologic changes in the heart in such diseases. In 35 fatal cases of myocarditis associated with acute nasopharyngeal and acute tonsillar infections seen at the Institute of Pathology there were extensive parenchymatous and interstitial inflammatory changes within the heart muscle.<sup>22</sup> Although bacteriologic data of the type utilized by Rantz, Boisvert and Spink were not available, the streptococcus was considered to be the most likely etiologic organism, and, as a matter of fact, it was found in throat cultures reported in 12 of the cases. Although these cases were considered to be clinically analogous to those described by Rantz and associates, the demonstrated anatomic changes in the heart do not support their conviction that such poststreptococcal carditis is essentially the same as that encountered in rheumatic fever<sup>23</sup> (Fig. 1, 2). Since acute nasopharyngitis and the cold are such commonplace infections, often not permitted to interfere with daily routine, one is tempted to wonder whether a proportion of sudden deaths hitherto reported as "isolated" or Fiedler's myocarditis are really properly diagnosed.



It would be very easy for the surviving relatives to omit mention of a recent "insignificant" cold. To be sure, death is still a rare complication of upper respiratory infection, but recognition of the much more frequent but milder degrees of myocarditis which may occur is of practical importance if death from this cause is to be prevented.

Surprisingly enough, the cardiac changes in *scarlet fever* do not resemble those just described. Among 40 fatal cases of scarlatina there were 27 (70 per cent) with demonstrable myocarditis on pathologic examination. Clinically the cardiac complication had been recognized in only ten. The very frequent presence of pneumonia, often with pleural effusion and pericarditis, and the occurrence of acute nephritis in one third of these cases understandably contribute to difficulty in properly evaluating ambivalent signs and symptoms such as chest pain, cyanosis, dyspnea, tachycardia, ascites and edema. Nevertheless the occurrence of these manifestations in the absence of pneumonia, pleurisy, or pericarditis; the development of conduction disturbance or arrhythmia, or unexpectedly sudden death cannot reasonably be explained on any other than a cardiac basis. Microscopically, the lesion, which has been well described by Brody and

Smith,<sup>24</sup> consists of a subendothelial and perivascular infiltrate of small round cells, and focal infiltrates of similar cells not characteristically located in the myocardium. In more than half the cases, especially in the severe ones, the focal infiltrates were associated with small foci of necrosis of an acute hyaline or granular type. This parenchymatous lesion, although never quantitatively as striking as that in diphtheria, followed the same pattern of evolution and healing. Bacteria were not found in the myocardial lesion (Fig. 3 and 4).

Myocarditis resulting from *diphtheria* has been a well-recognized entity for many years. Loeffler anticipated Roux and Yersin's demonstration of the potent toxin by reporting that the organism was not invasive but remained at the site of the local diphtheritic lesion. The principal effects of the toxin are upon the heart muscle and peripheral nerve. At one time the view that nerve changes were of prime importance in causing the myocardial effects was strongly championed, but the hypothesis never gained wide acceptance and is mentioned only because it is sporadically revived to becloud the true situation. Among 221 fatal cases of diphtheria at the Army Institute of Pathology, myocarditis was demonstrated at patho-

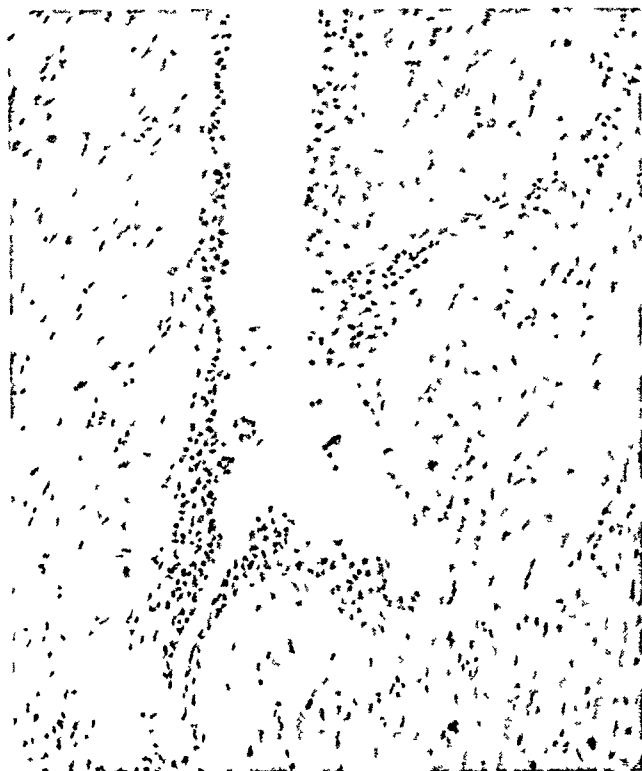


FIG. 3. Myocardial lesion in an adult male who died seven days after the onset of scarlet fever. Note the prominent subendocardial round cell infiltrate outlining a thebesian vessel. AIP Neg 95848,  $\times 135$ .

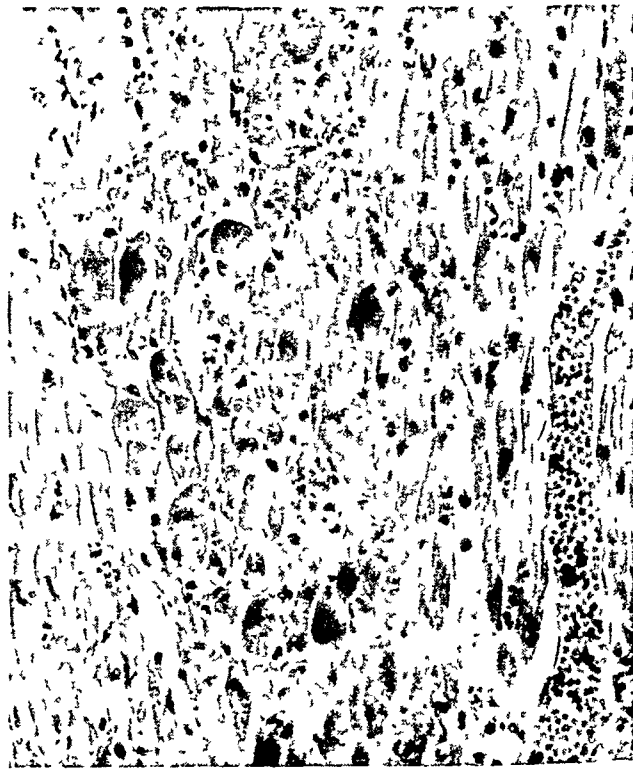


FIG. 4. Focal area of myocardial necrosis on the seventh day of scarlet fever. AIP Neg 95850,  $\times 275$ .



FIG. 5. Granular degeneration of the heart muscle following diphtheria of seven days' duration. AIP Neg. 93108,  $\times 230$ .

logic examination in 70 per cent and peripheral neuritis in 24.4 per cent. Both lesions showed a marked rise in frequency in relation to the length of survival from the onset of the acute illness, but myocarditis developed earlier and more frequently. The lesion consists of hyaline and granular degeneration of the heart muscle (Fig. 5). The myocardium shows patchy involvement and, with increasing length of survival, the degenerated muscle undergoes lysis; the reparative inflammatory process culminates in fibrosis. Although some authors object to classifying a primarily degenerative lesion as inflammatory, there appears to be no sharp distinction between the cellular reaction to such a lesion and the cellular response to parenchymal damage less obvious with current histologic technics.<sup>25</sup>

The postmortem demonstration in 1936 of myocarditis in two of ten fatal cases of *meningitis* paved the way for its clinical recognition.<sup>26</sup> By 1939, 13 cases had been reported in the literature.<sup>27</sup> Electrocardiographic evidence of transient heart damage was demonstrated in 1945<sup>28</sup> and again in 1946.<sup>29</sup> Holman and Angevine<sup>29</sup> reported a cardiac fatality 33 days after the onset of meningitis. At autopsy the primary meningeal infection proved to be entirely healed, but the myocardium showed the effects of an inflammatory process which had destroyed a consid-

erable portion of the musculature. In a review of 256 cases of acute meningococcemia at the Army Institute of Pathology, all were found to be complicated by acute myocarditis. The process was generally mild but widespread, involving the entire thickness of the myocardium, and was often somewhat more intense in the looser textured inner layers of the myocardium. Characteristic were marked interstitial edema and mild diffuse increase of large mononuclear cells in the stroma, sometimes masked by a perivascular infiltrate of polymorphonuclear leukocytes (Fig. 6). Small foci of acute muscle degeneration were frequently present although in exceptional cases large portions of the myocardium were involved (Fig. 7). Bacteria could be demonstrated, although with some difficulty in many instances. With the newer drugs such alterations in acute septicemia are no longer of only academic interest. Bacteriologic cure may be completely nullified by permanent cardiac residua. The physician must be aware of this possibility and remain alert for any cardiac manifestations so as to adopt proper preventive and corrective measures in time to avert a fatal outcome.

There are many other bacterial diseases in which a significant degree of myocarditis may occur, but time permits only a brief mention of them. *Tuberculosis*

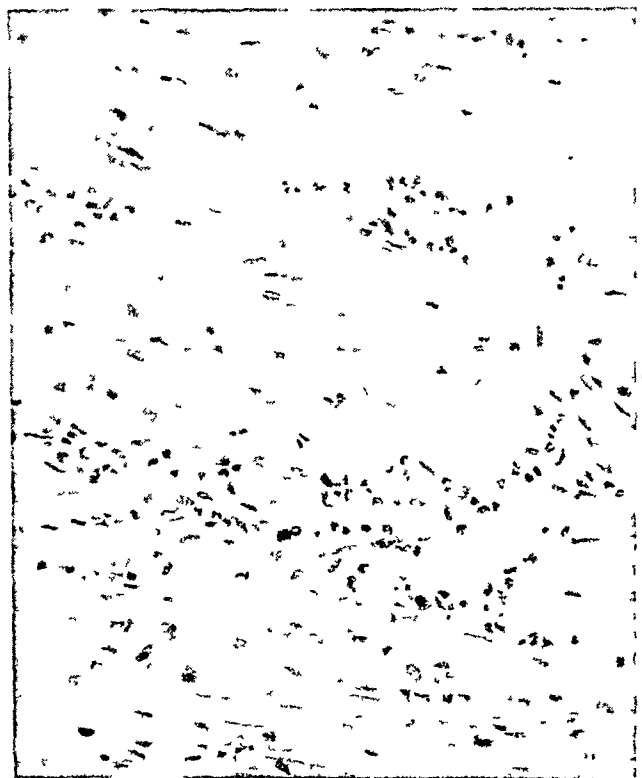


FIG. 6 Myocarditis in acute meningococcemia; note the diffuse interstitial edema and the mixed type of cellular inflammatory infiltrate. AIP Neg. 95855,  $\times 235$ .

has been reported to involve the myocardium in 0.28 per cent of adults and 3.9 per cent of children with the disease. Lesions were found in the heart in 15 per cent of cases of the miliary form.<sup>30</sup> Five hundred eighty one autopsies on adults who had died of tuberculosis were reviewed by Aronson at the A.I.P. There were specific lesions in the heart muscle in nine, all with the miliary form of the disease. Solitary tubercles were seen in five, tuberculous nodules in three, and tuberculoma (subendocardial) in one (Fig. 8).

Rickettsial diseases affected the myocardium frequently. In *scrub typhus*, a problem of the Southern Pacific campaigns, the heart was involved in all of 227 fatal cases. *Epidemic typhus* and *spotted fever* had caused myocarditis in about half of the cases which came to autopsy.<sup>31</sup>

Spirochetal infections other than syphilis undoubtedly affect the heart, as seen in a large proportion of autopsies in *Weil's disease* and *relapsing fever* in which the myocardial damage was of a degree to have been clinically significant (Fig. 9).

It is difficult to assay the importance of virus diseases as causes of myocarditis since bacterial infections so often complicate fatal cases. In well-controlled animal experiments, none of the viruses known



FIG. 8. Solitary tubercle in the myocardium of an adult male who died of miliary tuberculosis complicating advanced pulmonary disease. AIP Neg. 95843,  $\times 260$ .

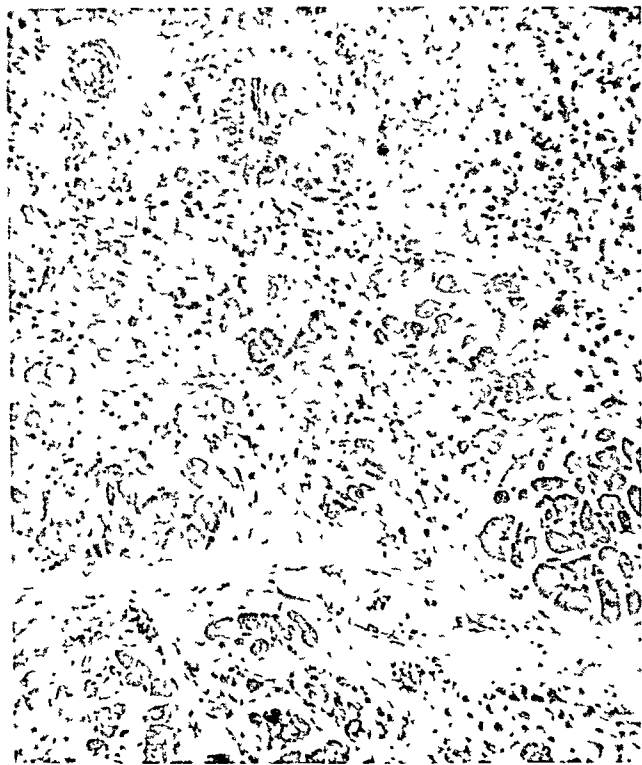


FIG. 7. Extensive myocardial degeneration which explained congestive heart failure in a young man who had had acute meningococcic meningitis 33 days previously. The meningitis had been cured. AIP Neg. 95847,  $\times 125$ . (Case previously reported by Holman and Angevine.)

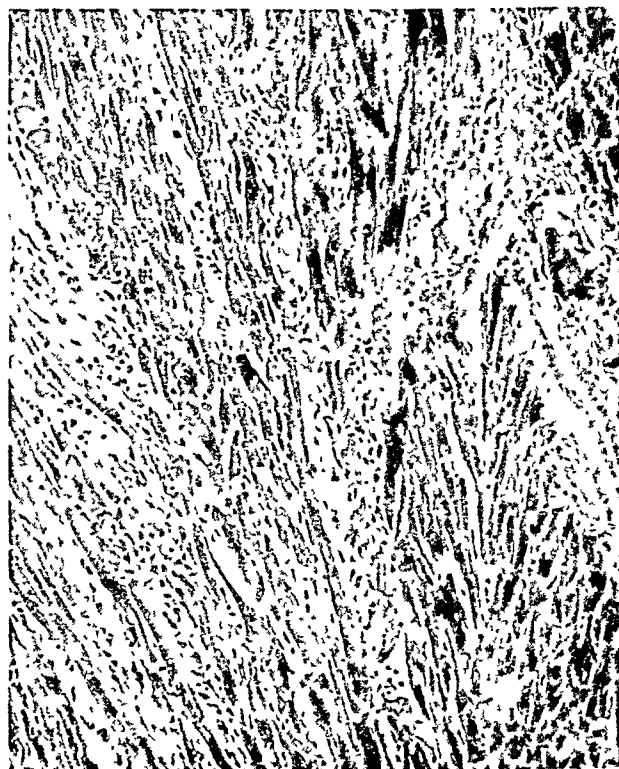


FIG. 9. Extensive interstitial myocarditis which contributed to death in a young Chinese with relapsing fever. Spirochetes were identified in the filtrate, with special stains. AIP Neg. 92526,  $\times 100$ .

to be pathogenic for man produced myocardial lesions. (A virus isolated by Helwig from spontaneous myocarditis in a chimpanzee consistently produced heart lesions in guinea pigs.<sup>32</sup>) In human material, however, significant inflammatory lesions of the heart muscle have been reported in influenza, atypical pneumonia (now known to be not a single etiologic entity) and poliomyelitis. The material at the Institute includes, in addition, examples of myocardial damage associated with acute encephalitis, infectious mononucleosis, measles, mumps, epidemic hepatitis and smallpox.

Parasitic infections producing myocarditis include trichinosis, malaria schistosomiasis, Chagas' disease, sarcosporidiosis and toxoplasmosis.

Generalized fungus infections identified as causing myocarditis include coccidioidomycosis (Fig. 10), blastomycosis, torulosis and actinomycosis.

Finally, hypersensitive states, typified by the sulfonamide reactions; physical injuries, such as burns and heat stroke; chemical poisoning, such as that from carbon monoxide; and metabolic disturbances occasioned by malnutrition, for example, are all capable of producing significant lesions in the heart.

It is only when all these diseases and injuries known to have etiologic significance have been ruled out that

we are correct in speaking of myocarditis as "isolated" or Fiedler's. With such careful selection the number of cases dwindles out of all proportion to the volume the discussion of this entity occupies in the literature.

Depending upon the duration of survival, the final pathologic picture regardless of its etiology is myocardial fibrosis which varies in degree with the extent of the original muscle damage (Fig. 11). Should there be extensive disease subendocardially, mural thrombi may form and lead to a prolonged and eventually fatal clinical course featured by repeated episodes of embolization. Boikan<sup>33</sup> has described this as pernicious myocarditis, but a similar syndrome has occurred following diphtheria, brucellosis and acute upper respiratory infections.

The clinical manifestations of postinfectious myocarditis have not been brought into this discussion to this point because they are common to all etiologic forms. Sudden death was frequent, but even among these cases there had been many which included premonitory clinical manifestations of heart disease. Cyanosis, dyspnea, orthopnea; cardiac irregularity; and disproportions of temperature and pulse, either tachycardia or bradycardia, were frequent. Shock and substernal pain or oppression were frequently observed and deserve particular emphasis since their significance as an index of failing circulation was not generally appreciated. In such a state there is considerable danger of further overloading the heart by the administration of intravenous fluids. Pulmonary edema was a common finding terminally, and among some of the less acute cases there were other evidences of congestive failure including enlarged and tender liver, ascites and dependent edema. The electrocardiogram was particularly valuable in detecting myocardial disease and in following its course. Abnormalities, which were the rule, included the arrhythmias, conduction disturbances, and changes in the configuration of the T-wave. Finally, attention must be drawn to a deceptive characteristic of postinfectious myocarditis: a so-called "healthy interval" of varying length after the etiologic infection seemed to have been controlled or healed. In a recent review of fatal cases of diphtheria for example, myocarditis in 25 per cent became manifest from 4 to 12 days after apparent recovery,<sup>25</sup> and in acute tonsillitis and nasopharyngitis a like percentage of cases displayed a similar latent period.<sup>22</sup>

From this brief survey of the material studied at the Army Institute of Pathology it is apparent that there are few cases of myocarditis in which a specific etiologic factor is not present. There are also few cases in which a specific etiology can be named from the microscopic changes alone. Such an assay usually re-

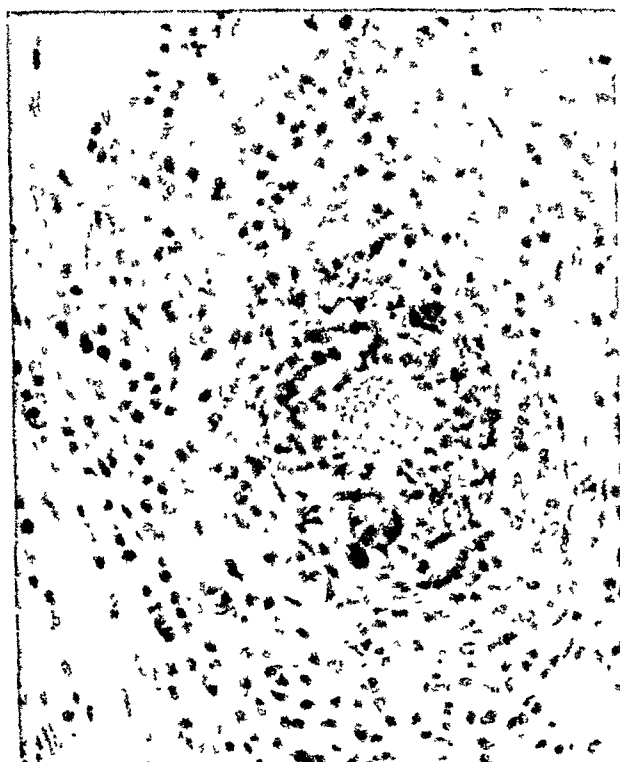


FIG. 10. Granulomatous lesion within the myocardium caused by and incidental to generalized coccidioidomycosis. Note the large spherule with numerous endospores. AIP Neg. 95812,  $\times 360$ .

quires a good clinical history, including the laboratory findings and a knowledge of the changes in tissues other than the heart.

### BIBLIOGRAPHY

1. White, P. D.: Heart Disease, ed. 2, New York, Macmillan, 1937.
2. Christian, H.: Osler's Principles and Practice of Medicine, ed. 14, New York, Appleton-Century, 1942.
3. Lewis, T.: Diseases of the Heart, New York, Macmillan, 1934.
4. Saphir, O.: Myocarditis, a review of 240 cases, Arch. Path., 32:1000, 1942.
5. Roelsen, E.: Electrocardiographic studies in scarlet fever, Acta med. Scandinav., 106:26, 1941.
6. Master, A. M., and H. Jaffe: Electrocardiographic evidence of cardiac involvement in acute disease, Proc. Soc. Exper. Biol. & Med., 31:931, 1934.
7. Master, A. M., A. Romanoff, and H. Jaffe: Electrocardiographic changes in pneumonia, Am. Heart J., 6:696, 1931.
8. Burnett, C. I., and G. F. Piltz: The electrocardiogram in acute infections, J. A. M. A., 94:1130, 1929.
9. Hyman, A. S.: Post-influenzal heart block, M. J. & Rec., 124:698, 1926.
10. Bang, O.: Gonorrheal myocarditis, Brit. M. J., 1:117, 1940.
11. Rosenberg, D. H.: Electrocardiographic changes in epidemic parotitis (mumps), Proc. Soc. Exper. Biol. & Med., 58:9, 1945.
12. Candel, S., and M. C. Wheelock: Acute nonspecific myocarditis, Ann. Int. Med., 23:309, 1945.
13. Rantz, L. A., W. W. Spink, and P. J. Boisvert: Abnormalities in the electrocardiogram following hemolytic streptococcus sore throat, Arch. Int. Med., 77:66, 1946.
14. Gore, I., and O. Saphir: Myocarditis, a classification 1402 cases. To be published.
15. Warthin, A. S.: The role of syphilis in the etiology of angina pectoris, coronary arteriosclerosis and thrombosis, and of sudden cardiac death, Am. Heart J., 6:163, 1930.
16. Magill, T. P.: Syphilitic myocarditis, Bull. Johns Hopkins Hosp., 57:22, 1935.
17. Clawson, B. V., and E. T. Bell: The heart in syphilitic aortitis, Arch. Path. & Lab. Med., 4:922, 1927.
18. Martland, H. S.: Syphilis of the heart and aorta, Am. Heart J., 6:1, 1930.
19. Saphir, O., and R. W. Scott: Observations on 107 cases of syphilitic aortic insufficiency with special references to the aortic valve area, the myocardium and the branches of the aorta, Am. Heart J., 6:56, 1930.
20. Saphir, O.: Syphilitic myocarditis (general review), Arch. Path., 13:436, 1932.
21. Scherf, D.: Myocarditis following acute tonsillitis, New York M. Coll. & Flower Hosp. Bull., 3:252, 1940.
22. Gore, I., and O. Saphir: Myocarditis associated with acute tonsillitis and acute nasopharyngitis. To be published.
23. Rantz, L. A., P. I. Boisvert, and W. W. Spink: The etiology and pathogenesis of rheumatic fever, Arch. Int. Med., 76:131, 1945.
24. Brody, H., and L. W. Smith: The visceral pathology in scarlet fever and related streptococcus infections, Am. J. Path., 12:373, 1936.
25. Gore, I.: Myocardial changes in fatal diphtheria: a summary of the findings in 221 cases. To be published.
26. Saphir, O.: Meningococcic myocarditis, Am. J. Path., 12:677, 1936.
27. Hartwell, R. M.: Meningococcic endocarditis and myocarditis, Am. J. Dis. Child., 58:823, 1939.
28. Rappaport, J. M., and M. Zuckerbrod: Recovery from fulminating myocarditis proved by electrocardiography, J. Lab. & Clin. Med., 30:307, 1945.
29. Holman, D. V., and D. M. Angevine: Meningococcus myocarditis, report of two cases with anatomical and clinical characteristics, Am. J. Med. Sc., 211:129, 1946.
30. Auerbach, O., and A. Guggenheim: Tuberculosis of the myocardium, a review of the literature and a report of six new cases, Quart. Bull. Seaview Hosp., 2:264, 1937.
31. Allen, A. C., and S. Spitz: Comparative study of the pathology of scrub typhus and other rickettsial diseases, Am. J. Path., 21:603, 1945.
32. Smadel, J.: Virus Division, Army Medical School, Personal communication, 1946.
33. Boikan, W. S.: Myocarditis perniciosa, Virchow's Arch. f. path. Anat., 282:46, 1931.

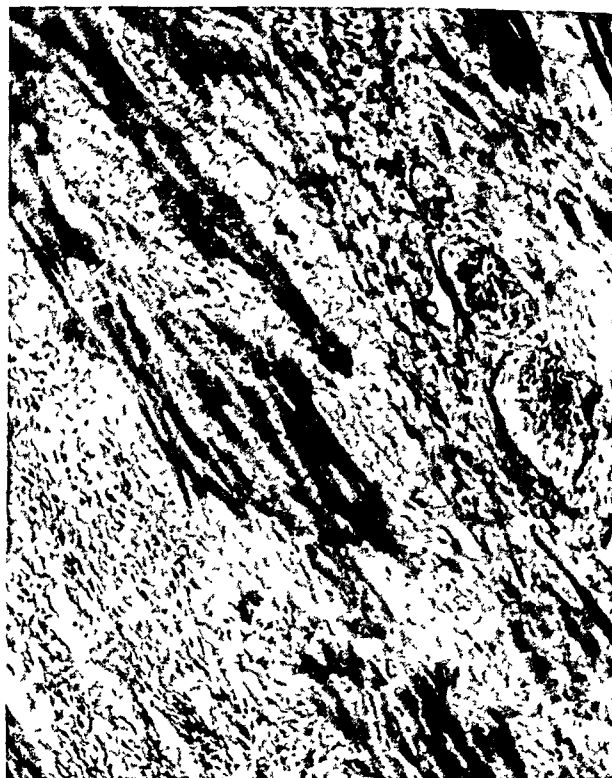


FIG. 11. Extensive myocardial fibrosis explaining sudden death in a young white man. Investigation revealed that the patient had had six recurrences of benign tertian malaria during a two-year period; the last, six months prior to death. Although one wonders about the etiologic significance of the malaria, the histologic alterations are no more specific than is scar tissue found elsewhere. AIP Neg. 95858,  $\times 150$ .

# The Present Status of Electroshock Therapy\*

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*Electroshock is being used extensively in certain psychiatric disorders with a high percentage of excellent results. Every physician should know the indications for such treatment so that he may select those who may be benefited by treatment.*

Electroshock therapy, or ECT as it is called, was first used in humans by Cerletti in 1938 in Italy.<sup>1</sup> Since then it has come a long way. It has definitely established its place in the therapeutic armamentarium of the psychiatrist. The apparatus used to induce shock has been perfected until practically fool-proof and the therapeutic indications have been delineated. It should be emphasized, however, that it is not a panacea for treatment of all forms of mental illness, that used improperly it is not without danger and that in itself it does not affect cures. It is a means to an end, not an end in itself. Its greatest use is in certain types of functional mental illnesses and since these are due to emotional causes it follows that unless we treat these emotional causes with psychotherapy, after the acute symptoms have been relieved by the ECT, the chances of a recurrence are very great.

The apparatus used to induce shock is fairly simple to use. The directions that come with the apparatus are quite explicit and there are enough safety devices incorporated to break the current should anything go wrong. The most popular type uses 50–60 cycle alternating current, 105–125 volts. Each treatment consists of passing about 400–500 milliamperes of current for 0.2–0.5 second through the patient's brain by means of electrodes applied to the temples. A special paste is applied in order to get better contact. Normally, the patient should have a grand mal convulsive seizure and this is followed by a period of stupor which varies in duration. ~

Shock therapy is still empirical but this should not detract from its worth, since it has proved its value by

pragmatic tests. Research is going on and one day, probably in the not distant future, its mode of action will be discovered.

## INDICATIONS FOR THE TREATMENT

The results with shock treatment are best in those cases that have been ill less than a year. As the duration of illness increases, the remission rate decreases.

Depressions of all sorts whether they be manic-depressive depressions, involutional melancholias or senile depressions give the best recovery rates with electroshock therapy.<sup>2-4</sup> It may be said to be the treatment of choice in these conditions. It is in these types of illness that a suicidal drive is normally found and to do away with this self-destructive tendency is the first objective in the treatment of these disorders. Electroshock does just this—the wish for suicide disappears after from two to four treatments. Usually these conditions require only eight or ten treatments. The remission rate for this type of illness treated by electroshock is quoted by various workers as from 80 to 100 per cent.<sup>3, 5</sup>

This type of therapy is also used in the excited or manic stage of manic-depressive psychosis. Usually about 15 treatments are required in this type and the results show that about 70 to 80 per cent of cases improve.<sup>3, 5</sup>

The results in dementia precox (schizophrenia) are not quite as good as those achieved in the affective disorders. It is best in those cases that have been ill less than six months. Usually the type benefited is that which has been diagnosed as the catatonic type. There is a large affective component in these cases. These cases usually require about 20 treatments. The remission rate usually quoted for cases of schizophrenia treated by electroshock is 60 to 70 per cent for those cases ill less than six months, about 40 per cent for those ill six months to two years and less than 10 per cent for cases in which the duration of illness is over two years.<sup>3, 5</sup>

Electroshock therapy is not as useful in psychoneurotic conditions as it is in psychoses. It is the treatment of choice in psychoneurotic reactive depres-

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sions but on the whole as a treatment for psychoneurotics it is disappointing. It has been used in the obsessive-compulsive states but with only temporary improvement.<sup>3, 5</sup>

It can be said, of course, that the types of mental illnesses most benefited by this form of treatment are those which in the old days before shock treatment would improve anyway. That is true. However, ECT shortens the course of the illness, decreases the length of hospitalization required and frequently avoids the suicides that used to occur while we were waiting for the patient to improve.

It should be emphasized that electroshock induces memory defects, which are most marked in the retentive sphere. Frequently for this reason patients may appear to be improved whereas actually they are not. The memory defect has simply blotted out their hallucinations and delusions. For this reason at Saint Elizabeths Hospital we usually wait for a month until we attempt to evaluate the results of treatment. By that time the memory defects have disappeared and we get a true picture of the patient's condition.

ECT should not be given the first day a patient enters a mental hospital. After all we are not sure of the diagnosis until he has been hospitalized for about 30 days. During that time hydrotherapy, chemotherapy and psychotherapy can be used and many cases will improve without recourse to ECT.

### CONTRAINDICATIONS<sup>3</sup>

As our experience with ECT grows, the number of contraindications to this form of therapy is being gradually reduced. Each patient has to be considered individually—the risks taken have to be balanced against the possible therapeutic gains. Age in itself is not a contraindication. Senile depressions in the eighth decade of life have been treated without difficulty. In those cases where a serious mental illness warrants the treatment, the psychiatrist must assume the responsibility for the additional risk as would the surgeon for an operative procedure in such patients.

The following conditions are usually considered contraindications to ECT.

1. Advanced heart disease
2. Recent coronary occlusion
3. Angina pectoris
4. Pulmonary tuberculosis
5. Malignancy
6. Bone disease
7. Arterial hypertension
8. Aneurysm of the aorta
9. Cerebral aneurysm and cerebral hemorrhage

10. Brain tumor and increased intracranial pressure
11. Exophthalmic goiter
12. Acute infections
13. Thrombophlebitis
14. Peptic ulcer
15. Intestinal diverticulae

Pregnancy is in itself not a contraindication. After all, seizures in epileptics do not result in abortion or premature birth. Hypertension due to emotional causes such as agitated depressions is lowered following improvement due to ECT. Myocardial disease does not contraindicate the treatment. Agitation represents a constant strain on the diseased heart and, therefore, improvement of the mental condition will lessen this strain. Chronic infections such as syphilis do not preclude this form of treatment.

### COMPLICATIONS<sup>3</sup>

A careful study of the mechanism of all possible complications has led to the prevention of many. The most frequent complications are fractures caused by the first sudden muscular contraction which takes place in ECT.

Compression fractures of the vertebral bodies are common. They usually occur between the fourth and eighth thoracic vertebrae. Many of these are found only on x-ray examination and actually cause no symptoms. When the patient does complain it is usually of back pain. Normally special treatment is not required for these fractures. The rates reported for this type of complication vary from 0.5 per cent (Taylor) to 20 per cent (Horowitz).

Long bones are seldom fractured by the convulsion. Fractures of the humerus, femur, acetabulum and ribs have been reported.

Dislocation of the jaw has been reported but not recently. Better technic in holding the jaw seems practically to have eliminated this complication.

Dislocation of the arm is a rare occurrence. Muscle tendons and ligaments seem rarely to be injured in convulsive therapy.

Apnea does occur as a physiologic phenomenon in any epileptic seizure.

Pulmonary abscess, gangrene of the lung and aspiration pneumonias have occurred. Activation of a latent tuberculosis may take place.

Cardiac arrest may occur but is infrequent.

Neurologic complications are practically unknown—hemiparesis has been reported.

Other complications that have been seen are rupture of a diverticulum, bleeding from a peptic ulcer, subconjunctival hemorrhages and nasal hemorrhages.



PREVENTION OF COMPLICATIONS<sup>3</sup>

A good physical examination and medical history reveals most contraindications. X-ray of the chest serves to exclude severe heart conditions, aortic aneurysm and pulmonary infections. An EKG is desirable but not indispensable. A lateral x-ray of the spine should be done routinely. Any laboratory studies indicated by the physical examination and history, such as BMR are carried out.

During the treatment the spine is hyperextended. This can be done with a surgical Gatch bed. The chin is grasped and thus dislocation of the jaw is prevented. A mouth gag is used to prevent biting of the tongue.

After the convulsion artificial respiration is used if necessary. The patient is allowed to inhale oxygen at the rate of eight liters per minute. The oxygen prevents headaches and vomiting.

Curare is used to prevent fractures. It does not paralyze the muscles completely but will soften the contractions sufficiently to prevent most fractures. Intocostrin (Squibb) a standardized preparation of curare is used. This contains 20 units of active curare per cc. The dosage is  $\frac{1}{2}$  unit per pound of body weight. The maximum dose is usually 4-5 cc. Curare is injected intravenously at a slow rate of 1 cc. per minute. After one or two minutes the ECT is given. After the convulsion the patient is given 1 cc. of 1:2,000 prostigmine intravenously. In case of failing respiration epinephrine is also given.

Curare is used most commonly in patients with previous fractures or bone diseases such as osteoporosis, Paget's disease, etc.

## FATALITIES

Kalinowsky reported on more than 2,000 cases without a fatality.<sup>3</sup> At Saint Elizabeths Hospital there was one fatality in over 1,000 cases. Kolb and Vogel in their survey of all American hospitals found a death rate of 0.06 per cent for ECT.

The number of fatalities is higher when curare is used and, therefore, the death may be attributed to the curare and not the ECT itself.

The exact mechanism of death following ECT is not clear. Experimental data, themselves divergent, do not correlate too well in humans, nor do observations of them show any great consistency. In cats, rabbits, dogs and rats, Alpers and Hughes, Heilbrun and Weil and Neuberger have observed petechial hemorrhages in the meninges, especially over the brain stem, in the cerebrum and cerebellum, associated with relatively little glial reaction but showing

indications of organization. The results in human cases are less informative due to the presence of such extraneous factors as age, cardiac complications and anoxia, long intervals between termination of treatments and death and complicating syphilis of the brain. However, there have been observed hemorrhages of small size and varying age scattered throughout the brain, scattered areas of cell loss and ischemic cell change and fat emboli.<sup>6</sup>

Brain pathology has rarely explained the cause of death. When death occurs it is usually of cardiovascular origin.

## AMBULATORY ECT IN PRIVATE PRACTICE

ECT is given by quite a few psychiatrists in their offices. Office treatment should be given only where the patient can rest, if necessary, for a few hours following the treatment. Postconvulsive excitement is the greatest problem in office treatment, making it necessary that appliances for mechanical restraint be available. Sodium amytal given intravenously may also be used for this purpose. The patient should be accompanied to the office. The most suitable patient for office treatment is the depressive who requires only a few treatments and thereby avoids commitment to an institution with all its social complications. The psychiatrist who treats patients in his office with this type of therapy should have particularly wide experience with the method since he usually has less help than at the hospital.

ELECTRONARCOSIS<sup>2</sup>

A current of from 160 to 260 milliamperes is applied and maintained for 30 seconds during which the patient has a tonic spasm, then reduced to 60 to 75 milliamperes at which time the patient has clonic contractions. The onset of respiration occurs at from 40 to 70 seconds and then 5 per cent oxygen is administered. The current is gradually raised (5 milliamperes/15 seconds) until an inspiratory stridor develops. If the stridor disappears the current is raised up to 125 milliamperes at 5 minutes. Treatment is ended at 7 minutes. Usually this treatment is used in schizophrenia.

## MAINTENANCE TREATMENT

This method is usually used in institutionalized cases to control behavior. It makes the patient easier to handle. Treatments are given once a week or every two weeks.



## SUMMARY

Electroshock therapy has established its place as a therapeutic tool in psychiatry. It is only a means to an end and must be used in conjunction with psychotherapy. It is most useful in affective disorders, can be helpful in the treatment of those cases of schizophrenia where there is a large affective component. It is of very little use in the treatment of psychoneurotics. The contraindications for this form of therapy are decreasing in number. A careful study of the mechanism of complications has led to the prevention of most. The use of curare where indicated helps to prevent certain types of complications. The number of deaths attributable to ECT is minimal. ECT can be used in office practice for treatment of properly selected cases.

## BIBLIOGRAPHY

1. Impastato, D. J., and R. Almansì: Electrically induced convulsions in the treatment of functional mental illness, *M. Ann. District of Columbia*, 10:163 (May) 1941.
2. Duval, A. M.: Treatment in psychiatry, *M. Ann. District of Columbia*, 15:363 (Aug.) 1946.
3. Kalinowsky, L. B., and P. H. Hoch: Shock Treatments and Other Somatic Procedures in Psychiatry, New York, Grune & Stratton, 1946.
4. Lewis, N. D. C.: What's what about shock therapy, *Ment. Hyg.*, 30:177 (April) 1946.
5. Gralnick, A.: A three year survey of electro shock therapy, *Am. J. Psychiat.*, 102:583 (March) 1946.
6. Alpers, B. J.: The brain changes associated with electrical shock treatment. A critical review, *Digest Neurol. & Psychiat.*, 14:136 (March) 1946.
7. Tietz, E. B., G. N. Thompson, Van Harreveld, and C. A. G. Wiersma: Electronarcosis—a therapy in schizophrenia, *Am. J. Psychiat.*, 101:821 (May) 1945.

## WHAT'S YOUR DIAGNOSIS?

A 67-year-old white woman was admitted to the Medical Service on 10/24/39 complaining of weakness, nausea and vomiting.

The time of onset of her illness was rather indefinite. She described slight weakness and some weight loss over the period of the previous year, and there were two brief episodes of extreme weakness. However, the patient was inclined to date the onset of her sickness to four months before admission when she underwent injection and ligation of varicose veins which had been present for several years in the left leg. Two days after the procedure she experienced for several days rather violent nausea and vomiting without fever or chills. Three weeks later, injection and ligation of veins of the right leg was followed by nausea and vomiting of two or three days' duration and accompanied by gaseous distension of the abdomen. The description of her subsequent course varies, but apparently she complained of constant mild nausea, without vomiting, and progressively increasing weakness. There was gradual and persistent swelling of the lower extremities and slight increase in the size of her abdomen. About one month before admission she was confined to her bed. At that time her physician thought that she had heart failure, and digitalized her without favorable results. Her nausea increased and

she began to vomit frequently and complained of extreme weakness. During the last three weeks she noticed that her tongue was sore and red. There was a 20 to 25 lb. weight loss. She had never been aware of exertional dyspnea or orthopnea. At no time during her illness was there any abdominal pain, diarrhea, melena, hematemesis, or evidence of jaundice. There were no urinary tract symptoms other than occasional periods of frequency during the last few years. It was said that her diet for many years had been deficient in proteins and meat. She described excellent general health prior to the onset of her illness, and she recalled no significant illnesses except for the usual childhood diseases.

Physical examination revealed a poorly nourished, aging woman who appeared weak and chronically ill and showed considerable evidence of recent weight loss. T. 98.6°, P. 96, R. 16. There was marked edema of the legs, thighs, back and lateral portions of the abdominal wall. No significant glandular enlargement was noted. The ocular fundi were not remarkable. The tongue was described as beefy red and smooth with atrophic papillae. There was no evidence of venous engorgement. The lungs were clear except for inconstant râles at both bases. The

heart was of normal size. The heart sounds were normal in quality. Faint, inconstant systolic murmurs were described at the mitral and pulmonic areas. One observer described a paradoxical pulse. B. P. 120/70. The radial arteries were not abnormally thickened. There were signs of a small amount of free fluid in the peritoneal cavity. The liver was considerably enlarged, extending down to the level of the umbilicus and it appeared that the enlargement was confined mostly to the right lobe. The surface was described as smooth and only slightly tender. The spleen was not palpable. No other abdominal masses or tenderness were made out. There were a few dilated veins over the lateral aspects of the abdomen

but these were not conspicuous. No hemorrhoids were noted and vaginal examination produced no remarkable findings. No neurologic abnormalities were evident.

During her course in the hospital she had no fever. There was a persistent tachycardia. She was put on a low-salt diet and treated with diuretics. Supplementary vitamins were given. Her course was uneventful and there was little change in her condition until the day before her death, when she complained of severe weakness and it was found that her blood pressure was unobtainable. This state persisted despite a transfusion of 500 cc. of whole blood and she died quietly on the ninth hospital day.

## LABORATORY DATA

Urine						
HOSP. DAY	SP. GK.	ALB.	SUGAR	MICROSCOPIC		CULTURE
1	1.025	3 +	0	Loaded with WBC. Occ. granular cast.		Sterile
1 (cath.)	0.021	3 +	0	Numerous hyaline, granular and cellular casts. 5-10 WBC and RBC.		
Blood						
HOSP. DAY	RBC	HGB.	WBC	DIFFERENTIAL	NPN	SERUM CHOLESTROL
1	6,300,000	17.7 Gm.	8,700	Seg. 73%, Lymph. 14%, Mono. 12%, EOS. 1%, Platelets normal	71	625
2	6,100,000	17.4 Gm.				625
3						3.48 (Alb. 1.58, Glob. 1.90)
7					92	
8					109	3.46 (Alb. 1.24, Glob. 2.22)

Kahn and Wassermann: Negative.

Blood sugar (fasting): 103 mg. per cent (1st Hosp. day).

Icterus index (1st Hosp. day): 3.

Uric acid (2nd Hosp. day): 6.8.

Basal metabolic rate (2nd Hosp. day):  $\pm 0$ .

Bromsulfonphthalein test (3rd Hosp. day): 56 per cent retention in 30 minutes.

P.S.P. test (2nd Hosp. day): 15 min.—no spec.; 30 min.—15 per cent; 1 hr.—15 per cent; 2 hr.—10 per cent.

Venous pressure (1st Hosp. day): In arm—105 mm. saline; in leg—95 mm. saline.

G.I. series (3rd Hosp. day): "No upper G.I. lesion."

Barium enema (6th Hosp. day): "No defect except for a few diverticulæ in the sigmoid."

Electrocardiogram (1st Hosp. day): Low voltage in lead 3.

(8th Hosp. day): Low voltage in all leads.

The correct diagnosis for the case which was presented in the December 1946 issue will appear in this space next month. There will be a tabulation of the number of correct diagnoses and the variety of those which went astray. The larger the number of diagnoses received the more interesting and instructive this feature will become. Send your diagnosis on a post card to Rudolph H. Kampmeier, Vanderbilt Hospital, Nashville 4, Tennessee. They need not be signed, but the case should be identified by the issue in which it appeared.

# EDITORIAL . . .

## Specialization and General Medicine

This editorial is prompted by a letter recently received from a subscriber who felt that the review of Elwyn's "Diseases of the Retina" in the October number of AMERICAN PRACTITIONER was useless because those in general practice have no time to read a book written "especially for the specialist in ophthalmology." Actually, as pointed out in the review, the book was written for the man in general practice as well as for the specialist. However, the importance of the letter is in the viewpoint expressed by its writer. Such a point of view, which unfortunately is too generally held, keeps physicians from learning things they should know and doing things they should do. It is a serious handicap to professional improvement and operates to keep the man in general medicine from filling to the full his proper and highly important place in medical practice.

It is true that the highly specialized technics of certain specialties are not the responsibility or even the permissible activity of the nonspecialist. There are, however, certain aspects of most, if not all specialties, with which he should, indeed must, be familiar if he is to practice properly. These usually include the simpler aspects of diagnosis and prognosis in the specialty, the recognition of certain abnormalities in that field, a knowledge of their meaning and what should be done about them. Much less often does it include doing something about them, for specialties are built largely on procedures for treatment and therein specialism finds much of its proper place.

No better example of all this is to be found than in ophthalmoscopy, which in a large measure deals with diseases of the retina. Here is a specialized procedure which is of the greatest importance in the diagnosis, and particularly in the early diagnosis, of many diseases which the general practitioner should recognize.

Often, the diagnosis in the early stages can be made by ophthalmoscopy alone, and, as pointed out in the review, the procedure is simple. Much of it is easily within the capabilities of any man practicing general medicine. Usually he is the one to see the patient first. On him depends the early diagnosis of diseases, which, if undetected, may cause irreparable damage. How else will the man in general medicine make these diagnoses at the time he should? How else will he detect certain brain tumors before eyesight is lost; how else control the treatment of central nervous system syphilis with certain drugs? What about hypertension, one of the commonest of serious diseases of the present day, and the significance of retinal changes in relation to prognosis and the indications for treatment by sympathectomy?

It is not meant that every physician should become an expert ophthalmologist. But, there are so many important abnormalities, so easily learned and detected in this manner, and others to be at least suspected, that no physician should be considered properly trained or to be practicing properly unless he is familiar with them. If he is already acquainted with ophthalmoscopy and its findings to this extent, the study of a text on diseases of the retina may not be worthwhile. If he is not, such a book should be secured and studied at the first opportunity. The old, semihumorous definition of the difference between the specialist and the general practitioner, that the former makes rectal examinations and looks at the eye-grounds, still is more than a little true. If the gap between specialists and general practitioners is ever to be narrowed, as it should be, ophthalmoscopy is one of the things the man in general medicine must do. It is up to him.

# The Clinical Analysis of 550 Cases of Bacterial Meningitis\*

## Diagnostic Features and Various Methods of Treatment

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*The reader will find this to be an excellent review of diagnostic points and discussion of the results of treatment by chemotherapeutic and antibiotic agents.*

The incidence of meningococcus meningitis has increased ten-fold in the past three years.<sup>1</sup> Interest in the disease has been enhanced by the numerous reports, chiefly from hospitals of the armed services, of excellent results in therapy with the various sulfonamides and penicillin.<sup>2</sup> While this report adds little new information, it affords a fairly comprehensive picture of meningitis as encountered in civilian practice for comparison with that seen in the service groups. Also, it demonstrates the fact that other types of purulent meningitis occur frequently, so that proper therapy must depend upon establishing the etiologic diagnosis.

### INCIDENCE OF VARIOUS TYPES

All of the patients with meningitis entering Cook County Contagious Disease Hospital between Decem-

ber 1, 1943 and September 1, 1946 were studied. It will be seen (Table 1) that 71.5 per cent were diagnosed as meningococcic meningitis. In all likelihood most of the cases of unidentified purulent meningitis were likewise caused by meningococci. That the proportion of meningococcus cases has greatly increased is shown by the fact that in a previous report<sup>3</sup> of meningitis at this same hospital between January 1, 1937 and February 1, 1940, the ratio of meningococcus meningitis to pneumococcus meningitis was 105 to 71 in contradistinction to the present ratio of 393 to 46, and the ratio of *H. influenzae* meningitis was 105 to 29 as compared to 393 to 15 in the present study. It is interesting that in the period of the present study, no cases of hemolytic streptococcus meningitis were encountered.

### DIAGNOSIS

The etiologic diagnosis of purulent meningitis can be determined with certainty only by finding the organism in direct smears or cultures of the spinal fluid,

TABLE 1  
*Meningitis at Cook County Contagious Hospital  
Mortality Regardless of Treatment  
December 1, 1943 to September 1, 1946*

ETIOLOGY	CASES	LIVED	TOTAL DIED	DIED LESS THAN 24 HOURS AFTER ADMISSION	TOTAL	CORRECTED
					MORTALITY %	MORTALITY %
Meningococcus	393	319	74	33	19	11.38
Unknown	66	62	4	1	6	4.6
Pneumococcus	46	14	32	13	70	57.87
<i>H. influenzae</i>	15	7	8	1	53	50.00
Tuberculous	16	0	16	0	100	100.00
Green streptococcus	9	4	5	2	56	45.7
Green streptococcus and meningococcus	2	1	1	0	50	50.00
<i>B. coli</i>	2	0	2	0	100	100.00
Staphylococcus	1	0	1	0	100	100.00
Total cases	550					

\* From the Department of Medicine, Northwestern University Medical School, Chicago, Ill.

in direct smears of petechial hemorrhages of the skin, or in blood cultures. In the present series meningococcemia was assumed if there was meningitis accompanied by petechial hemorrhages in skin or mucous membranes, even if the organisms were not demonstrated. The diagnosis was made in this way in 64 cases. In all other instances, except tuberculous meningitis the diagnosis was made by positive smears or cultures of the spinal fluid or by blood cultures. The diagnosis of tuberculous meningitis was made in the usual way by finding fluid with a clear or "ground glass" appearance, with a cell count in the hundreds, mostly lymphocytes and from which there was no growth on ordinary culture media. Such fluids usually had typical "pedicles" of fibrin agglutination. In such patients there were signs of basilar involvement, the most characteristic of which was strabismus. In every instance, the Mantoux test was positive, and often there was a history of pulmonary or joint tuberculosis. As noted in the table, all these patients died and in five, the diagnosis was confirmed at autopsy. In those in which guinea pig inoculations of the spinal fluid were made, tuberculous lesions resulted in the test animals.

The cases of purulent meningitis were so similar in their clinical manifestations at the onset, that unless petechiae were present even a tentative etiologic diagnosis usually had to be postponed until the results of bacteriologic studies were known.

### MENINGOCOCCIC MENINGITIS

As noted above, the large majority of the cases of meningitis entering Cook County Contagious Hospital were of this type. In a few instances in children, high fever and petechial hemorrhages of the skin were the only entering complaints. Rarely in the latter cases, especially among infants, there were no signs of meningeal irritation. However, practically all the patients had rigidity of the neck and a positive Brudzinski's and Kernig's sign. Petechial hemorrhages of the skin were present in 63.08 per cent of the meningococcus cases. Stained smears of blood from petechial hemorrhages were made in only a few instances. They were usually positive for meningococci. The value of searching for the causative organisms in *all* ways is emphasized by the figures in Table 2.

### MORTALITY

The mortality in meningococcus meningitis and meningococcemia in our series (Table 1) is high as compared with that in most other reported series, practically all of which were smaller and in selected

groups. In analyzing the cause for this several factors which influence the outcome were studied.

TABLE 2

#### Diagnostic Findings in 393 Cases of Meningococcus Meningitis

	PER CENT OF TOTAL
Petechiae of skin present	63.08
Meningococci in gram stain of spinal fluid	64.63
Meningococci in cultures of spinal fluid	69.28
Spinal fluid culture was only positive bacteriologic finding	5.09
Meningococci in blood cultures (of those cultured)	37.39
Per cent in which positive blood culture was only bacteriologic finding	7.37
Petechiae present in the absence of any bacteriologic findings	16.28
Results of typing of meningococci—149 cases.	
Type I	Type II
142 (95.30%)	2 (1.34%)
	Type II-A
	4 (2.61%)
	Type IV
	1 (0.67%)

TABLE 3

#### Meningococcus Meningitis

#### Mortality in Various Groups with Regard to Age

AGE GROUP	TOTAL CASES	DIED			MORTALITY	
		DIED -1 da. Rx	DIED AFTER 1 da. Rx		GROSS %	COR- RECTED %
Under 3	57	7	5	2	12.28	3.84
3-10	76	8	7	1	10.53	1.45
11-20	67	3	2	1	4.48	1.54
21-30	52	4	2	2	7.69	4.00
31-40	50	16	5	11	32.00	24.44
41-50	37	12	4	8	32.43	24.24
51-60	37	16	6	10	43.24	32.22
61-70	12	4	2	2	33.33	20.00
71-80	5	4	0	4	80.00	80.00
Totals	393	74	33	41	18.83	11.38

**Influence of Age of the Patient.** In Table 3 it is seen that in the patients above 30 years old, the mortality rose sharply over that of the previous decades. Mortality in the decades 10 to 20, and 20 to 30 years compares favorably with reports from the armed services on patients in similar age groups. Thus it appears that, as in pneumonia and most other acute infections, the outlook is much more favorable in children beyond infancy and in young adults than in patients beyond 30 years of age.

**Time Elapsing before Treatment Was Begun.** It was our clinical impression that delay in instituting treatment was a very important factor in causing an unfavorable outcome. However, this could not be proved statistically. Among those who recovered, in 63 per cent the illness had lasted three days or less, prior to entering the hospital, while in the group who died, the duration of illness before admission was

three days or less in 69 per cent. A factor which is very important, but cannot be accurately considered, is the treatment received prior to entering the Contagious Disease Hospital. In all likelihood, more of those who recovered had had sulfonamide treatment of some kind prior to entrance, than of those in the fatal outcome group, but the proof of this surmise is lacking. This factor plus the inherent virulence of the infection, was probably the deciding factor in the outcome rather than delay in entering the hospital.

The majority of those who died came to the hospital delirious or in deep coma and never regained consciousness. As noted in Table 1, 33 of the 74 deaths occurred within 24 hours of admission. Four of these died before any treatment could be given and 13 had only one dose of the sulfonamide used. None had more than three doses. Since this is clearly inadequate treatment, the patients dying within the first 24 hours are not listed in the "corrected" mortality figures. Eighteen died on the second day of hospitalization. Several of these also had had not more than three doses of sulfonamide or less than 100,000 units of penicillin. Thus 39 of the 74 patients who died survived less than 48 hours after being brought to the hospital.

**Influence of Associated Morbid Changes.** This feature is difficult to evaluate because so many of the patients died before a proper study of their complete physical status could be made and a necropsy was done on only 39 of the 74 who died. However, it is clear that degenerative changes, particularly hypertension, heart disease and nephritis played a dominant role in the fatal outcome in the group above age 30. The blood pressure was not taken in the majority but in those in whom it was recorded, a definite hypertension was present in 14, the range being 140 to 210 systolic, and 100 to 120 diastolic. In these persons pulmonary edema and decompensation were frequently associated findings. Bronchopneumonia was a frequent autopsy finding but only three had frank pneumonia on admission. Nineteen had advanced inactive rheumatic heart disease as evidenced by characteristic murmurs, cardiac enlargement, auricular fibrillation and, in some instances, decompensation. Three had hemorrhagic nephritis as shown at autopsy. The majority of those in the fatal outcome group who survived long enough to have urine examinations done had red cells in the urine. Whether this was due to the disease itself or to sulfonamide medication, of course, is difficult to determine. In two instances *sulfonamide intoxication* appeared to be the cause of death.

It is interesting that among the 15 deaths of chil-

dren under 11 years, only three lived more than 48 hours after being brought to the hospital. All had fulminating meningococcemia and were practically moribund in admittance. Twelve died within 24 hours. Five had the clinical picture of the Waterhouse-Friedrichsen syndrome but there was an autopsy on only three of them. In each of these three patients hemorrhages in the bowel, pleural and pericardial surfaces as well as the adrenals were present. One of the children had acute glomerulonephritis.

**Significance of Positive Blood Cultures and Petechiae.** The mortality was higher in those with positive blood cultures than in the negative blood culture group, but the difference was not as great as we had expected. In all, 246 patients had blood cultures prior to beginning their active treatment. In 37.39 per cent the culture revealed meningococci. The gross mortality in this group was 18.47 per cent as against 16.23 per cent in the group with negative blood cultures. Probably there is a transient bacteremia in all cases of meningococcal systemic infections. Abundant evidence reveals all parts of the body affected and in children, especially, the localization in the meninges may be a relatively unimportant part of the total picture.

We were surprised, also, to find that the occurrence of petechiae in the skin did not parallel the finding of meningococci in blood cultures. As noted previously, petechial hemorrhages were noted in 63.08 per cent of our patients. These varied greatly in number and size, some being so extensive that they formed large ecchymoses from which areas of skin up to 10 cm. in diameter sloughed away. Even in such cases the blood culture was not always positive. In the patients with petechiae who were studied the blood culture was positive in 37.39 per cent, while in those without petechiae, 35.4 per cent had positive blood cultures. The mortality in the group with petechiae was 20.37 per cent as against 17.39 per cent in the ones who had none.

**Significance of the Spinal Fluid Findings.** On some of the services at Cook County Contagious Hospital, no spinal puncture is done if the clinical picture, including petechial hemorrhages, makes the diagnosis of meningococcemia fairly certain. However, in more than 90 per cent, a spinal puncture was made. The initial cell count was usually in the thousands, and in general the higher the cell count, the worse was the prognosis (Table 4). The danger of discounting a diagnosis of bacterial meningitis because of the fact that the cell count was not in the thousands is illustrated in Table 4. In the fatal meningococcus group, 11.6 per cent had total initial cell counts under 1,000,

TABLE 4  
*Meningococcus Meningitis*  
*Spinal Fluid Cell Counts and Glucose Levels*

Average spinal fluid cell count in recovered group	7,900
Average spinal fluid cell count in fatal group	16,000
Cell counts under 1,000	Recovered group 15.0%
	Fatal group 11.6%
Average spinal fluid glucose level in recovered group	18.1 mg. per 100 cc.
Average spinal fluid glucose level in fatal group	9.5 mg. per 100 cc.

and in two cases, the count was below 100. In the recovered group 15 per cent had cell counts under 1,000 and in eight cases it was below 100.

Spinal fluid glucose determinations were made in the majority of cases, and again the well-understood fact that the lower the glucose level the worse the prognosis was illustrated. As we had found in a previous study of pneumococcus meningitis, a high bacterial content with a relatively low cell count in spinal fluid smears presaged a bad outcome for the patient.

**Significance of the Leukocyte Count of the Blood.** The leukocyte count of the blood was recorded regularly on the service of the author. Ninety-nine cases were thus studied and the counts followed the pattern that was anticipated. The average initial leukocyte count in the fatal cases was 18,300, the figure being in the normal range of 6,000 to 9,000 only once. In the recovered cases, the average initial leukocyte count was 19,000. An initial leukopenia was recorded only once and a first count in the normal range, five times. In all these instances except one, the patient developed a leukocytosis later on. In practically all of the patients with an initial leukocytosis who recovered, serial counts made at intervals of two days, showed a progressive drop in total leukocytes. In all patients in whom a differential count was made, there was a predominance of polymorphonuclear leukocytes.

#### TREATMENT

Treatment was carried out under the direction of resident physicians who changed at intervals of two to six months, by internes who changed every month. Hence, the doses administered were not always the same. Nine patients received penicillin alone. All the other treated patients received sulfonamides or a combination of sulfonamides with penicillin. The majority of the patients received sulfathiazole or its sodium salt, because this was the only sulfonamide

issued by the drug department of Cook County Contagious Hospital for this disease. On the service of the author, sulfathiazole was not used unless treatment had already been started with this drug before the patient came to the Contagious Disease Hospital. Through the courtesy of Sharp and Dohme, enough sulfamerazine was obtained to treat 40 cases with this drug entirely, and 10 more received sulfamerazine as part of their treatment. Sulfadiazine was obtained from the Illinois State Health Department for the treatment of a small series.

**Treatment with Sulfathiazole.** Practically all of the patients received the drug intravenously on the first and second days after admission, after which time the maintenance dose of sulfathiazole was given by mouth as soon as the subject was able to swallow it. The plan of treatment varied somewhat on the different services but in adults usually an initial dose of 5 to 8 Gm. was given intravenously, followed at intervals of four to six hours by maintenance doses of 2 to 3 Gm. After oral doses were tolerated usually 1.0 to 2.0 Gm. every four hours were given (Table 5). The

TABLE 5  
*Meningococcus Meningitis*  
*Average Doses of Sulfonamides and Penicillin*

AGE GROUP	SULFATHIAZOLE	SULFAMERAZINE	SULFADIAZINE	PENICILLIN
Under 3				
Initial dose	2.6 Gm.	2.02 Gm.	1 Gm.	
Maintenance dose per day	4.0 Gm.	3.8 Gm.	4.0 Gm.	
Total dosage	36.1 Gm.	24.5 Gm.	33.0 Gm.	
3-10				
Initial dose	3.7 Gm.	3.7 Gm.	5.0 Gm.	
Maintenance dose per day	4.8 Gm.	3.9 Gm.	5.3 Gm.	120,000 U.
Total dosage	35.5 Gm.	23.9 Gm.	45.0 Gm.	490,000 U.
Adults				
Initial dose	5.8 Gm.	5.2 Gm.	5.0 Gm.	
Maintenance dose per day	9.1 Gm.	5.5 Gm.	10.0 Gm.	100,000 U.
Total dosage	57.2 Gm.	50.3 Gm.	50.6 Gm.	743,000 U.

average total dose of sulfathiazole was 57.2 Gm. The doses for children were relatively higher for the age group concerned than for adults. In those cases in which blood and spinal fluid levels were taken the same day, the spinal fluid level was approximately one half the blood level (Table 6). The highest blood level was 43.2 mg. per cent, and in this case the patient died of sulfathiazole intoxication. In two other patients levels of 30 mg. and 23 mg. per cent, respectively, were attained. Both patients were toxic but did not die.

TABLE 6  
*Meningococcus Meningitis*  
*Sulfonamide and Penicillin Blood and Spinal Fluid Levels*

	AVERAGE HIGHEST BLOOD LEVELS ATTAINED PER CASE	COMPARISON OF BLOOD AND SPINAL FLUID LEVELS DETERMINED ON THE SAME DAY	
		BLOOD	SPINAL FLUID
Sulfathiazole	8.38 mg. per 100 cc.	6.08 mg. per 100 cc.	2.04 mg. per 100 cc.
Sulfamerazine	23.07 mg. per 100 cc.	21.9 mg. per 100 cc.	13.08 mg. per 100 cc.
Sulfadiazine	17.41 mg. per 100 cc.	13.11 mg. per 100 cc.	9.22 mg. per 100 cc.
Penicillin	0.29 Units per cc.	0.29 Units per cc.	0.19 Units per cc.

TABLE 7  
*Meningococcus Meningitis*  
*Relation of Mortality to Treatment*

	TOTAL CASES	LIVED	DIED LESS 24 HOURS	DIED AFTER 24 HRS. RX.	MORTALITY	
					GROSS	CORRECTED
Sulfathiazole	227	196	2	29	13.6	12.89
Sulfamerazine	44	42	1	1	4.5	2.32
Sulfadiazine	25	22	1	2	12.0	4.18
2 or 3 different sulfonamide	25	22	0	3	12.0	12.0
Penicillin alone	9	7	0	2*	22.2	22.2
Penicillin and sulfonamide	35	30	0	5**	14.3	14.3

\* One of these deaths was in a patient who received penicillin only intravenously, not intrathecally, 100,000 Units on each of 2 successive days.

\*\* Only one of these received penicillin intrathecally.

In Table 7 it is seen that the corrected mortality rate with the sulfathiazole-treated cases was 12.89 per cent.

**Treatment with Sulfamerazine.** In the sulfamerazine treated group, the plan was about the same except that when the maintenance dose was given intravenously the plan was to divide it into three doses of approximately 2.0 Gm. each given every eight hours. When administered by mouth, 1.0 to 2.0 Gm. was given every six hours. As in the sulfathiazole series, children were given relatively larger doses per kilogram of body weight than adults. On the service using sulfamerazine, the instructions were to give 16 to 22 Gm. of sodium bicarbonate orally every 24 hours or two liters of one-twelfth molar sodium lactate solution intravenously every 24 hours to increase the alkalinity of the urine and hence render it capable of keeping more of the drug in solution. For the most part these instructions were carried out. In 12 of the 40 patients treated with sulfamerazine, the blood levels ranged from 25 mg. to 77.21 mg. per 100 cc., but with a urinary pH of 7.5 or over, obtained by the alkalinizing dosage mentioned, no renal blocking was observed. In Table 6 it is seen that in spite of lower initial and maintenance doses of sulfamerazine, much higher blood levels were obtained and the ratio of spinal fluid to blood level (when both were taken the same day) was somewhat higher.

**Treatment with Sulfadiazine.** The series treated with sulfadiazine alone is too small to offer a fair basis of comparison with the other sulfonamides. It will be noted that in spite of larger daily maintenance doses, the sulfadiazine cases had blood levels lower than the patients treated with sulfamerazine, but higher than with sulfathiazole. In the instances in which blood and spinal fluid levels were determined the same day, the ratio of spinal fluid level to blood level was higher than with sulfamerazine.

**Reactions to Sulfonamides.** Reactions to sulfonamide therapy were surprisingly few, especially when one considers the size of the dosage required and that, except on one service, sodium bicarbonate was not administered regularly with it. The explanation probably is that an abundant fluid intake by the patients was seldom neglected, the plan being to give adults 2,000 to 3,000 cc. daily and children corresponding doses. In the early stages of the disease it was necessary to give most of this intravenously.

There were two instances in which it is almost certain that sulfonamide intoxication played a major role in the patients' deaths. A fifteen-month-old child entered the hospital on the second day of his attack of meningitis. He was reported to have received 2.5 Gm. of sulfadiazine prior to admission. He was given 2.0 Gm. of sulfathiazole the night of admission and 6.0 Gm. the following two days. After



that, the dose was 3.0 Gm. for three more days, the entire dosage being 26.0 Gm. of sulfathiazole. No sodium bicarbonate was given with it. Two days after admission the sulfathiazole blood level was 43.2 mg. per cent. He developed anuria, went into uremia and died on the eighth day of his illness. At autopsy the meningitis was found to have cleared up. There were massive deposits of sulfonamide crystals in the renal calyces and tubules and minute cortical abscesses in both kidneys. Also found were scattered patches of bronchopneumonia, cardiac dilatation and parenchymatous degeneration of the heart muscle, passive congestion of the liver and infectious hyperplasia of the spleen.

A 51-year-old woman was admitted on the second day of her attack of meningitis. She was given 5 Gm. of sodium sulfathiazole on admission and a total of 12 Gm. daily thereafter until a total of 49 Gm. had been given. At this time she was started on penicillin *intravenously*, receiving approximately 200,000 units daily until a total of 1,135,000 units had been given. On her fifth hospital day, she was started on sulfadiazine, receiving in all 45 Gm. during her remaining six days of life. The urine was not alkalinized, and it had many red blood cells in it from the start. Marked oliguria occurred for three days before she died on the twelfth day of her illness. Necropsy revealed a subsiding purulent meningitis. There were many small focal cortical hemorrhages of the cerebrum surrounded by small areas of encephalomalacia. In the kidneys were found small parenchymal hemorrhages and petechial hemorrhages of the renal pelvis. Hemorrhagic cystitis was present and the bladder contained precipitated sulfadiazine crystals.

The height of the blood levels reached in the sulfamerazine cases with relative freedom from trouble is of interest. However, the patients whose levels reached 77.21 mg. per cent, 64 mg. per cent, and 45.3 mg. per cent respectively, all had red blood cells and crystals in the urine in spite of good alkalinization. In none did anuria or any other complication occur.

There was a prolongation of the prothrombin time in the majority of the meningococcus meningitis cases, regardless of the type of treatment. The possible role of the sulfonamides in this change will be discussed in another communication.

**Treatment with Penicillin.** Because of the shortage of penicillin at the time this study was proceeding, this agent was used chiefly as an adjunct to sulfonamide treatment. Since it was released for use only in patients who were not doing well on sulfonamides, the group receiving penicillin plus sulfonamides is a

selected one. As seen in Table 7, the mortality in this group was 14.3 per cent.

It was possible to treat only nine patients with penicillin alone. Seven of these recovered and two died. The ages of the ones who died were 75 and 5 years respectively. In the former, the factor of advanced age possibly would have been too great a handicap for any type of treatment to overcome. The other patient was in an age group where the outlook is better. However, the five-year-old child who died received the drug *intravenously* only, and died on the second day after receiving a total of 200,000 units. No spinal fluid assay for penicillin activity was made in this case. However, in two other patients receiving penicillin up to 200,000 units daily only *intravenously* for other diseases, it was not possible to demonstrate penicillin in the spinal fluid at all. This confirms the reports of other authors that penicillin seldom enters the spinal fluid from the blood stream in appreciable amounts.

Among the seven patients on penicillin therapy alone, who recovered, all were given the drug *intrathecally*. The general plan was to give adults 10,000 to 20,000 units *intrathecally*, mixed in 5 to 10 cc. of physiologic solution of sodium chloride after removing an amount of spinal fluid, at least double the volume of penicillin solution injected. This was administered on admission and repeated daily until the spinal fluid cultures remained sterile after 24 hours incubation. At the same time, the remainder of 200,000 units was given *intramuscularly*, divided into eight (three hourly) doses or *intravenously* over each 24 hours until the acute stage was over. Then a maintenance dose of 100,000 units was given *intravenously* or *intramuscularly* until the patient had been afebrile several days. This amount was reduced for the children. The average number of days of treatment was 7.5 days and the average total dose was 700,000 units per case. Using the method of Heilman, the average assay for penicillin in the blood on this dosage was 0.29 unit per cc. The average spinal fluid penicillin level, after 10,000 units injected the previous day, was 0.19 unit per cc. Although the series is too small for clinical conclusions, we had the impression that the drop in temperature and improvement in the other clinical features were less prompt with penicillin than with sulfonamide therapy.

One of the patients, a 32-year-old man, returned two and one half weeks after apparent recovery on penicillin management, with another attack of meningococcus meningitis. Relapse in the same fashion was observed in one patient apparently cured after treatment

with sulfathiazole, and another after clinical cure with sulfadiazine. No complications of penicillin treatment were observed.

### EXPERIENCE WITH PNEUMOCOCCUS MENINGITIS

In the present group, 13 patients died within 24 hours of admission, none of whom received more than two doses of sulfonamide and in 6 of whom death occurred before *any* type of treatment could be given.

While pneumococcus meningitis is often a primary disease it usually is secondary to, or associated with pneumococcus infections in other parts of the body. The associated pathologic changes are almost always purulent otitis media, extensive confluent pneumonia, or vegetative endocarditis. The prognosis depends on many factors but chiefly upon the extent and type of these associated changes. The chances of recovery are best in those patients in which the disease is "primary," that is, where the pneumococcus lesion is localized to the meninges and to the mucous membranes of the nose, throat and paranasal sinuses. The next best outlook is in these cases which appear to result from otitis media. When the meningeal involvement is associated with extensive pneumococcus pneumonia, the prognosis is much worse. When the meningitis is a part of the picture of pneumococcus vegetative endocarditis, the outlook appears to be hopeless, regardless of treatment. In the pneumococcus meningitis patients who survived long enough for a blood culture to be taken, the culture was positive in every instance.

Other circumstances associated with the pneumococcus meningitis cases are of interest. Among those who recovered, in all but four treatment was started within the first 48 hours of illness. In the remaining recovered cases, treatment was begun in all by the fourth day of illness.

Among the group who died, there was no history of the date of onset in nine of the moribund cases. In the remainder, the average duration of meningeal symptoms before treatment was four days, but the necropsies in most instances, revealed extensive changes which were obviously present many days before meningeal symptoms were recognized.

Age also appeared to play a role. In the recovered group the average age was 29 years, the oldest recovered patient being 45 years old. In the fatal group, the average age was 52 years, more than half of the patients being beyond 50 years and only one being under age 30.

Another observation which we had made previously

and which was confirmed in the present series, was that a low spinal fluid cell count with a relatively large number of pneumococci, in direct smear, gave an extremely bad prognosis, while a relatively high cell count with few or no organisms seen on smear was usually associated with a more favorable outcome. In 11 of the fatal cases, the spinal fluid cell count was less than 1,000, while it was above this figure in all of the recovered cases, averaging 4,600. The average cell count of the fatal cases was 1,800.

All combinations of treatment described previously for meningococcus meningitis were tried, and where possible, type specific pneumococcus antiserum was given also. As previously stated, 13 of the series of 46 cases died on the day of admission, six before any type of chemotherapy could be administered. Seven had one dose of a sulfa drug and the other patient had two doses of sulfathiazole.

While 7 of the 14 recovered cases received one of the sulfa drugs alone, our impression is that a combination of sulfamerazine, or sulfadiazine in full doses intravenously plus penicillin intrathecally is the treatment of choice. When the causative pneumococcus can be identified, early specific antipneumococcus serum is a valuable adjunct to therapy.

Among the 32 patients dying of pneumococcus meningitis, 20 succumbed within 48 hours after they were brought to the hospital. Of the remaining 12, two survived 20 days and one lived 13 days. In two of these, acute vegetative endocarditis was present and the meningitis was only one of the embolic features of the disease. The occasional relatively long survival of certain patients with pneumococcus meningitis with eventually a fatal termination is one of the disturbing features of the disease. In cases where the febrile period is prolonged many days past the time of expected recovery or death, one should be suspicious of vegetative endocarditis, unresolved pneumonia or brain abscess.

### H. INFLUENZAE MENINGITIS

H. influenzae meningitis is a disease of very young children, and rarely affects adults. Our series proved no exception, the oldest child in the group being five years old.

The prognosis appears to depend upon the age more than any other factor. In the fatal cases (eight in number), the average age was 16 months, the youngest infant being two months old and the oldest three years. In the recovered group (seven in number), the youngest child was two years and the oldest five years, the average age being three years. It is also noteworthy that in the fatal group the spinal fluid glucose

was too low to read in all but one patient, in this one case being 25 mg. per cent. On the other hand, the spinal fluid glucose ranged from 30 to 79 mg. per cent in the recovered group, averaging 49 mg. per cent. The average cell count was 4,400 in the group which died, and 3,200 in those who recovered.

In treatment, Alexander's rabbit serum was used in addition to sulfonamides and penicillin, whenever the serum could be obtained. Four of the five patients who recovered received the serum, but the largest total dosage given was 100 mg. Two of those who died had received serum, one having 25 mg., and the other 50 mg. All were given one or more of the sulfonamides in the dosages outlined for meningococcus meningitis and one patient in each group received intrathecal penicillin.\*

It was felt that the combination of sulfadiazine in full doses plus serum in as large doses as possible offered the best outlook for the patient. Either because the reaction to invasion of the meninges by *H. influenzae* excites a less violent reaction than some of the other incitants of purulent meningitis, or because of the age of the patients, the systemic manifestations are often milder than in the other types of meningitis. However, the prognosis is distinctly worse than in meningococcus meningitis and unless treatment is prosecuted vigorously for several days after the temperature has returned to normal, relapses are apt to occur. Streptomycin in doses of 2 to 4 Gm. daily, 100,000 units being given intrathecally, is now the agent of choice.

Four of the patients who died had postmortem examinations. In addition to the extensive purulent meningitis covering the hemispheres—which grossly appeared identical with that of meningococcus and pneumococcus meningitis—there was found, in every instance, advanced parenchymatous degeneration of the heart muscle, liver and kidneys, acute hyperplasia of the spleen and in two instances, extensive bronchopneumonia.

### STREPTOCOCCUS VIRIDANS MENINGITIS

*Streptococcus viridans* was established as the etiologic agent of purulent meningitis by spinal fluid culture in 11 instances. In two of these, the patients died within 24 hours of admission and neither had an autopsy. In one case, both meningococci and *Streptococcus viridans* were cultured from the spinal fluid and in another both organisms were present in the blood culture.

\* Since this series was compiled, three patients with *H. influenzae* meningitis have been successfully treated with streptomycin.

It has been our experience prior and subsequent to the present series, that *Streptococcus viridans* meningitis is nearly always a sequel of cerebral embolism in subacute bacterial endocarditis or of otitis media, the latter being more common in children. Only one of the cases of this series came to autopsy. In this instance, subacute bacterial endocarditis was found.

### STAPHYLOCOCCUS MENINGITIS

This condition was encountered only once in the present study and the etiology proved only at autopsy. Organisms with the morphology of staphylococci were seen in the spinal fluid smear but cultures of the spinal fluid and blood gave no growth.

On admission the patient was semicomatose and extremely toxic. She had been ill several days. Crackling râles were heard over both lung bases and a to-and-fro murmur over the mitral and aortic areas. There were many subconjunctival hemorrhages.

Postmortem examination revealed bronchopneumonia of the left lower lobe, metastatic abscesses in the parietal and occipital lobes with secondary leptomeningitis in these areas. There were multiple septic infarcts in the liver, spleen, both kidneys and myocardium, but the origin of the septicopyemia was not determined. The patient received 22 Gm. of sulfathiazole after admission over a three-day period, but without benefit.

### TUBERCULOUS MENINGITIS

While tuberculous meningitis cannot properly be classified as purulent meningitis, the 16 cases listed are discussed because they were encountered during the period covered by this study. There was often difficulty in differentiating them from the other types because, as stated previously, the spinal fluid cell count was below 1,000 in 10 to 15 per cent of the other cases.

The cell counts ranged between 120 and 800, averaging 350. In all but one instance the spinal fluid glucose was too low to read. During the time there was some doubt as to the diagnosis sulfonamides were administered to some of the patients without benefit. All died in the hospital, the longest hospital stay being 17 days.

### MENINGITIS OF UNDETERMINED ETIOLOGY

Fifty cases belonged in this category. In each instance there were no petechiae, smears and cultures of the spinal fluid and cultures of the blood were negative, and the clinical picture did not correspond to that of tuberculous meningitis.

In this series there were only four deaths—a distinctly better mortality rate than in the other groups. In all but one case, in which the autopsy revealed multiple abscesses of the brain with basilar meningitis and abscesses of the lungs, the clinical course was the same as that most often observed in meningococcic meningitis. Since meningococcus meningitis was proved in the large majority of cases in this series, it seems fair to assume that most of the unidentified cases were of this type also.

The reason for the more favorable result in this group probably is that bacteria were not growing in sufficient numbers to be observed or cultured in the spinal fluid or blood, indicating a high degree of resistance on the part of the patients, many of whom were partially recovered when they were hospitalized.

### B. COLI MENINGITIS

In both cases of this series, *B. coli* was cultured from the spinal fluid and in one case from the blood. One patient died two hours after admission and the other 19 hours after admission. The one autopsied had a severe urinary tract infection secondary to prostatic hypertrophy with trabeculation of the bladder and bilateral bronchopneumonia. Streptomycin was not available for their treatment.

### COMMENT ON TREATMENT

From the experiences outlined above, the importance of making an etiologic diagnosis in meningitis should be obvious, as treatment must be individualized. Also it has been pointed out that a spinal fluid cell count below 1,000 by no means rules out bacterial meningitis.

When first seen, a quick assay of the various factors which so profoundly influence the prognosis should be made. Besides the etiologic agent, these include delay in treatment; presence or absence of shock; associated morbid changes, such as rheumatic heart disease, bronchopneumonia, hypertension, cardiorenal disease, infective endocarditis; age of the patient; presence or absence of bacteria in the blood.

A plan of procedure appears in the accompanying outline.<sup>4</sup> In the author's opinion, sulfamerazine is the sulfonamide of choice. Sulfadiazine is more effective than sulfathiazole. In severe cases of meningococcus, pneumococcus or streptococcus meningitis, sulfamerazine or sulfadiazine along with penicillin administered intrathecally every 24 hours, constitutes the best treatment.

In *H. influenzae* meningitis, streptomycin, supplemented by sulfamerazine or sulfadiazine and Alexander's rabbit serum is the best treatment now available.

### SUMMARY

In a series of 550 consecutive cases of bacterial meningitis studied at Cook County Contagious Hospital from December 1943 to September 1946, all of the usual types were encountered, but meningococcic meningitis constituted 71.5 per cent of the cases.

The importance of making an etiologic diagnosis and evaluating those factors which influence mortality is emphasized.

Treatment of the various types of bacterial meningitis was more successful with sulfamerazine and sulfadiazine than with sulfathiazole.

Penicillin used alone appeared to cure seven of nine cases. It was used chiefly in conjunction with sulfonamides, both intrathecally and intramuscularly.

*H. influenzae* meningitis was treated with sulfonamides plus Alexander's rabbit serum with 50 per cent mortality. Since this report, three cures with streptomycin have been observed. Streptomycin appears to be the single most effective agent in this disease, but at present should be used in conjunction with sulfonamides and Alexander's rabbit serum.

#### PLAN FOR TREATMENT OF BACTERIAL MENINGITIS

1. Make an etiologic diagnosis if possible.
  - a. Spinal fluid smear, spinal fluid culture, blood culture.
  - b. Complete blood count.
  - c. Look for petechiae—meningococcus meningitis.  
(Meningococci often found in smears from petechial hemorrhages.)
  - d. Look for otitis media.  
Important atrium of infection in: streptococcus meningitis, pneumococcus meningitis, staphylococcus meningitis.
  - e. Look for symptoms and signs of active endocarditis.  
Important for diagnosis and prognosis in: streptococcus meningitis, pneumococcus meningitis.
  - f. Examine lungs carefully.  
Important in: pneumococcus meningitis, tuberculous meningitis.
2. For patients in shock:
  - a. Plasma or whole blood intravenously.
  - b. Adrenal cortical extract in full doses.
  - c. Oxygen if cyanotic.
  - d. Neosynephrin hypodermically.
3. General measures:
  - a. Fluids to 3,000 cc. daily by mouth or intravenously (adult).
  - b. Drainage of foci of infection, such as otitis media or acute sinusitis.
  - c. Sedative for patients who are extremely restless.  
Paraldehyde; ether in oil, per rectum; sodium phenobarbital or sodium amytal, subcutaneously.

4. Give *penicillin* in meningococcus, pneumococcus, streptococcus viridans, streptococcus hemolyticus, staphylococcus meningitis.

20,000 units dissolved in 5 to 10 cc. physiologic solution of sodium chloride intrathecally, after withdrawing 10 to 15 cc. of spinal fluid. Repeat every 24 hours until spinal fluid remains sterile on culture.

25,000 to 40,000 units every three hours, by continuous intravenous drip, or intramuscularly until spinal fluid and blood remain sterile on culture. Doses up to 1,000,000 units daily if the patient has bacterial endocarditis.

5. Give *streptomycin* in *H. influenzae* and *B. coli* meningitis.

100,000 units intrathecally every 24 hours. 1,000,000 to 4,000,000 units intravenously every 24 hours, or in divided doses every three hours intramuscularly.

6. Sulfonamide therapy:

For *H. influenzae*, meningococcus, pneumococcus, streptococcus viridans, streptococcus hemolyticus, staphylococcus meningitis, meningitis of undetermined etiology.

- a. *Sulfadiazine* (adult dosage).

1st dose—6 Gm. intravenously.

Maintenance dose per day—2 Gm. every 6 to 8 hours intravenously, or 1 to 2 Gm. every 4 hours by mouth.

or

*Sulfamerazine* (adult dosage).

1st dose—4 to 6 Gm. intravenously.

Maintenance dose per day—2 Gm. every 8 hours intravenously, or 1 to 2 Gm. every 6 hours by mouth.

- b. *Sodium bicarbonate* (adult dosage).

3 Gm. every 4 hours by mouth, or 1,000 cc. of 1/6 molar sodium lactate solution every 24 hours, intravenously.

7. Biologic therapy:

- a. For pneumococcus meningitis (adult dosage):

Type specific antipneumococcus rabbit serum 200,000 or 300,000 units intravenously during the first 12 hours—after ocular and cutaneous tests for sensitivity. Then 100,000 to 200,000 units per 24 hours until recovery begins.

- b. For *H. influenzae* meningitis:

Type B anti-influenzae rabbit serum 50 to 100 mg. as first dose, intravenously. Then 25 to 50 mg. every 24 hours until patient's serum gives capsule swelling reaction with *B. influenzae*.

- c. For meningococcus meningitis not responding to penicillin or sulfonamides: antimeningococcus serum intravenously or intrathecally.

## BIBLIOGRAPHY

1. U. S. Public Health Rep., Supplement No. 190, 1944.  
U. S. Public Health Rep., Apr. 7, 1944, p. 469.  
Statistical Bulletin, Metropolitan Life Insurance Co., Vol. 24, Nov. 8, 1943.
2. Goldring, D., A. F. Hartmann, and R. Maxwell: Diagnosis and management of severe infections in infants and children: meningococcal infection, *J. Pediat.*, 26:1 (Jan.) 1945.  
Grieco, E. H., and A. M. Cove: Meningococci meningitis—sulfadiazine therapy, *Ann. Int. Med.*, 21:194 (Aug.) 1944.  
Glaser, K.: Meningococcal meningitis, review of 100 cases, *Am. J. Dis. Children*, 68:116 (Aug.) 1944.  
Bohan, J. L., and F. B. Lusk: Diagnosis and treatment of epidemic cerebrospinal meningitis, *J. Lab. & Clin. Med.*, 29:585 (June) 1944.  
Meads, M., H. W. Harris, B. H. Samper, and M. Finland: Treatment of meningococcal meningitis with penicillin, *New England J. Med.*, 231:509 (Oct. 12) 1944.  
Osborne, J., W. H. Arnone, and G. I. Lythcott: Meningococcus meningitis and meningococcemia in childhood, *New England J. Med.*, 231:868 (Dec. 28) 1944.  
McCarty, A. C., and G. L. Infield: A report of 80 cases of meningitis, *Kentucky Med. J.*, 41:348 (Oct.) 1943.  
Rosenberg, D. H., and P. A. Arling: Penicillin in the treatment of meningitis, *J. A. M. A.*, 125:1011 (Aug. 12) 1944.  
Denny, E. R., R. G. Bausch, and M. A. Turner: Meningococcal infections, *Am. J. Med. Sc.*, 208:478 (Oct.) 1944.  
Whitaker, W. M.: Meningococcal infections, *U. S. Naval Med. Bull.*, 43:650 (Oct.) 1944.
3. Rhoads, P. S., A. L. Hoyne, B. Levin, R. G. Horswell, W. H. Reals, and W. W. Fox: Treatment of pneumococcal meningitis, *J. A. M. A.*, 115:917 (Sept. 14) 1940.
4. Rhoads, P. S.: Clinical features and treatment of bacterial meningitis. To be published in *Med. Clinics of N. America*.

# Gastro-intestinal Allergy

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*The diagnosis of gastro-intestinal allergy probably is made more often than it occurs. This paper presents aspects of the problem.*

Gastro-intestinal allergy is most frequently seen in the child up to the age of five. It is encountered in the adult most often in the cases of urticaria and angioedema. Asthma in the adult, contrary to most popular conceptions, is not a disease caused by foods to any great extent.

To understand food allergy, one must first understand the mechanism of the allergic reaction. Patients are divided into two groups, the first having immediate reactions, in whom we find the ingestion of food followed within a period of 15 minutes to one hour by clinical symptoms. This type of patient gives positive skin reactions and has circulating in the blood stream positive skin-sensitizing antibodies. The patients most frequently seen in this group are children having asthma caused by food and some of those having urticaria, and very few with gastro-intestinal allergy. The second group consists of patients having a delayed reaction and in these, ingestion of the food is followed by an interval varying anywhere from one to 72 hours between intake and the appearance of symptoms. These patients do not give positive skin reactions and do not have circulating in their blood stream skin-sensitizing antibodies. Most of the instances of gastro-intestinal allergy and many of those of angioedema occur in this group.

It is important to remember that, if the child has a food sensitivity, it usually lasts until he is five years of age, and then, due to causes not quite understood, there is a spontaneous involution of that type of sensitivity and a replacement by an inhalant type of sensitivity. Thus 98 per cent of food-sensitive children lose that sensitivity by the time they are five or six years old spontaneously and without any type of therapy. This is the explanation for the infrequency in occurrence of food allergy in the adult asthmatic patients.

In the infant, gastro-intestinal allergy makes itself apparent in the form of colic, pylorospasm, cyclic vomiting and vague abdominal pain. The most common

foods at fault are milk, eggs, and wheat. It is important to point out, however, that a great many children are apt to give wheat reactions on skin test. However, when these reactions are corroborated by the clinical test of feeding wheat, we find to our surprise that many of these children do not give any untoward response, and that the wheat reaction has no significance as a food, but frequently has a great deal of significance as an inhalant. Cows' milk is one of the most frequent causes of trouble in the infant. It is likewise possible for a child to be sensitive to breast milk, as human milk can convey various allergens to the nursing infant. This is also true in cows' milk and it has been shown by several observers that constituents of wheat, flaxseed, peanuts, and cottonseed may pass intact into cows' milk. The clinical symptoms produced by these allergens are not due to sensitivity to the milk but to these unaltered proteins contained in it.

Children who are sensitive to milk may be sensitive either to the whey fraction or to the casein in the milk. The albumen or whey fraction seems to give the most positive reactions although the casein is occasionally involved. As heat alters the lactalbumen to a considerable extent, it is occasionally possible for milk-sensitive children to take evaporated milk when raw milk cannot be tolerated. Patients sensitive to the whey fraction only can tolerate goat milk in the majority of cases. However, when they are sensitive to the casein portion of the milk, either alone or in conjunction with the lactalbumen, it is essential that substitutes be used. The best of these are the soybean substitutes, especially "Mulsoy." Numerous other synthetic substitutes have been tried with varying degrees of success. Sensitivity to cheese is not frequent, and is the result of sensitivity to casein. Patients mildly sensitive to milk may eat reasonable quantities of cheese products without symptoms. The cheeses which are made of whey and contain relatively large amounts of lactalbumen are the most allergenic. These are cottage cheese and cream cheese.

Eggs are a fairly frequent cause of trouble in the child, both in the production of gastro-intestinal allergy as well as of asthma. The treatment in the egg-

sensitive cases lies entirely in elimination of eggs from the diet.

In view of the fact that 98 per cent of these food allergies in children undergo spontaneous involution, the entire treatment of gastro-intestinal allergy depends on accurate diagnosis and subsequent avoidance of the allergen in question. Under no circumstances should any attempt be made at desensitization as, first, it is ineffectual and, second, when improvement results, it is almost invariably the result of a spontaneous involution of the sensitivity. In the adult, gastro-intestinal allergy may take the form of abdominal distress, burning and flatulence. Care must be exercised, however, in the willingness to ascribe the symptoms to allergy. I feel that too often vague signs of indigestion are promptly labeled allergy without any conclusive proof. The proof depends on the ability to reproduce symptoms at will within the same time limit on each clinical trial. X-ray studies of food-sensitive individuals have revealed an irritability of the entire gastro-intestinal tract, probably the result of edema of the lining of the mucosa.

In the cases of angioedema which are so commonly seen in the adult, the most frequent causes are fish, sea food, nuts and, of course, milk and eggs. Why it is that an adult will go many years with complete tolerance to certain foods and then suddenly become

sensitive to them, with resulting angioedema, is something that has puzzled all observers. The most frequently accepted explanations depend on the temporary permeability of the gastro-intestinal tract. Why this varies from time to time is difficult to say. Some observers feel that there is an element of skin refractoriness which explains the periods of supposed tolerance to the food. The fact remains, however, that these skin allergies do occur with a great degree of frequency; they rarely give positive skin reactions; and their mechanism is one of the delayed type. Contrary to the opinion voiced in much of the literature, the adult asthmatic patient is rarely sensitive to foods.

Today, with the antihistaminic drugs, we can give the cases of angioedema at least temporary symptomatic relief to a degree that was not possible a short time ago. In this connection, it is important to point out that every effort should be made to determine the cause of trouble while giving symptomatic treatment. In many cases, epinephrine in oil is quite effective.

The treatment of all gastro-intestinal allergies is, of course, elimination of the offending food or foods from the diet.

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### Infant Mortality

Infant mortality declined further in 1946 from the low rate for 1945, the U. S. Public Health Service, has announced. Provisional figures for the first ten months of 1946 indicate a decrease of 3.2 per cent from the rate for the same period of 1945.

Final figures for 1945 released at this time show that the infant mortality rate of 38.3 deaths under 1 year per 1,000 live births was the lowest ever recorded for the United States. It is 3.8 per cent lower than the rate of 39.8 for 1944. Infant deaths numbered 104,684 in 1945 as compared with 1944 when there were 111,127 deaths under 1 year.

The maternal mortality rate of 2.1 per 1,000 live births for 1945 also showed a reduction of nearly 9 per cent from the rate of 2.3 for the previous year. The numbers of deaths from puerperal causes on which the maternal mortality rates are based were 5,668, and 6,369, respectively, for 1945 and 1944.

One of the factors contributing to the lower infant and maternal mortality rates is an increase from 1944 to 1945 in the proportion of babies delivered in hospitals. In 1945, 78.8 per cent of all births registered in the United States were reported to have occurred in hospitals or other institutions. This represents an increase of 3.2 per cent from 1944 when 75.6 of recorded births took place in hospitals.

# Renal Complications in Children Receiving Sulfonamide Drugs\*

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*Four cases are described as examples of untoward effects of sulfonamides upon the kidneys.*

The frequency of untoward reactions following administration of sulfonamide drugs has been reported to be about 5 per cent in patients of all age groups; some authors have found an incidence as high as 25 per cent and others an incidence below 2 per cent. Fink and Smith<sup>1</sup> of Detroit, in a series of over 5,000 infants and children treated with sulfathiazole, sulfadiazine and sulfamerazine, noted less than 1.4 per cent of important complications of any type and serious renal disturbances in less than 1 per cent of patients. The maintenance dosage of sulfadiazine used in their patients was 1 grain per pound of body weight per day with half the total daily requirement given as an initial dose.

The significant complications were found to be of three main types:

1. Systemic, manifested by fever and skin rash.
2. Changes in the blood and blood-forming organs.
3. Renal complications.

All of these reactions might occur together; in fact, skin rash from sulfonamides very seldom occurred without fever. Gastro-intestinal and neurologic manifestations not infrequently were attributed to drug reactions; but since these systemic symptoms almost always appeared within the first or second day of drug administration, it was difficult to determine whether the symptoms were due to the sulfonamide or to the disease for which it was being used. Fever and rash, occurring during the initial course of chemotherapy, usually made their appearance between the fifth and ninth days; with subsequent doses of the same sulfonamide in a sensitized individual, these reactions occurred within the first 24 hours. Leukopenia, anemia, jaundice and purpura had their greatest incidence in the first two weeks; hematuria, oliguria and anuria within the first week.

Patients who developed sensitivity to one of the sulfonamides, such as skin rash from sulfadiazine, usually did not show any reaction to another of the

sulfonamide drugs such as sulfathiazole; but over one half of the patients reacting to one course of a sulfonamide developed "immediate" reactions to tests with repeat doses of the same drug. "Immediate" reactions were observed only in those patients who had shown previous drug sensitivity. (These authors did not find skin testing of suspected sulfonamide-sensitive patients with human sulfonamide-containing serum useful in children, but from their experience, did recommend observation of the patient after oral administration of a 0.25 Gm. dose of the suspected sulfonamide as a test for drug sensitivity.)

In the above mentioned series, the reactions characterized by fever, with and without rash, were most numerous. But the only two deaths were from renal shutdown with obstruction in the calices and ureters found on postmortem examination.

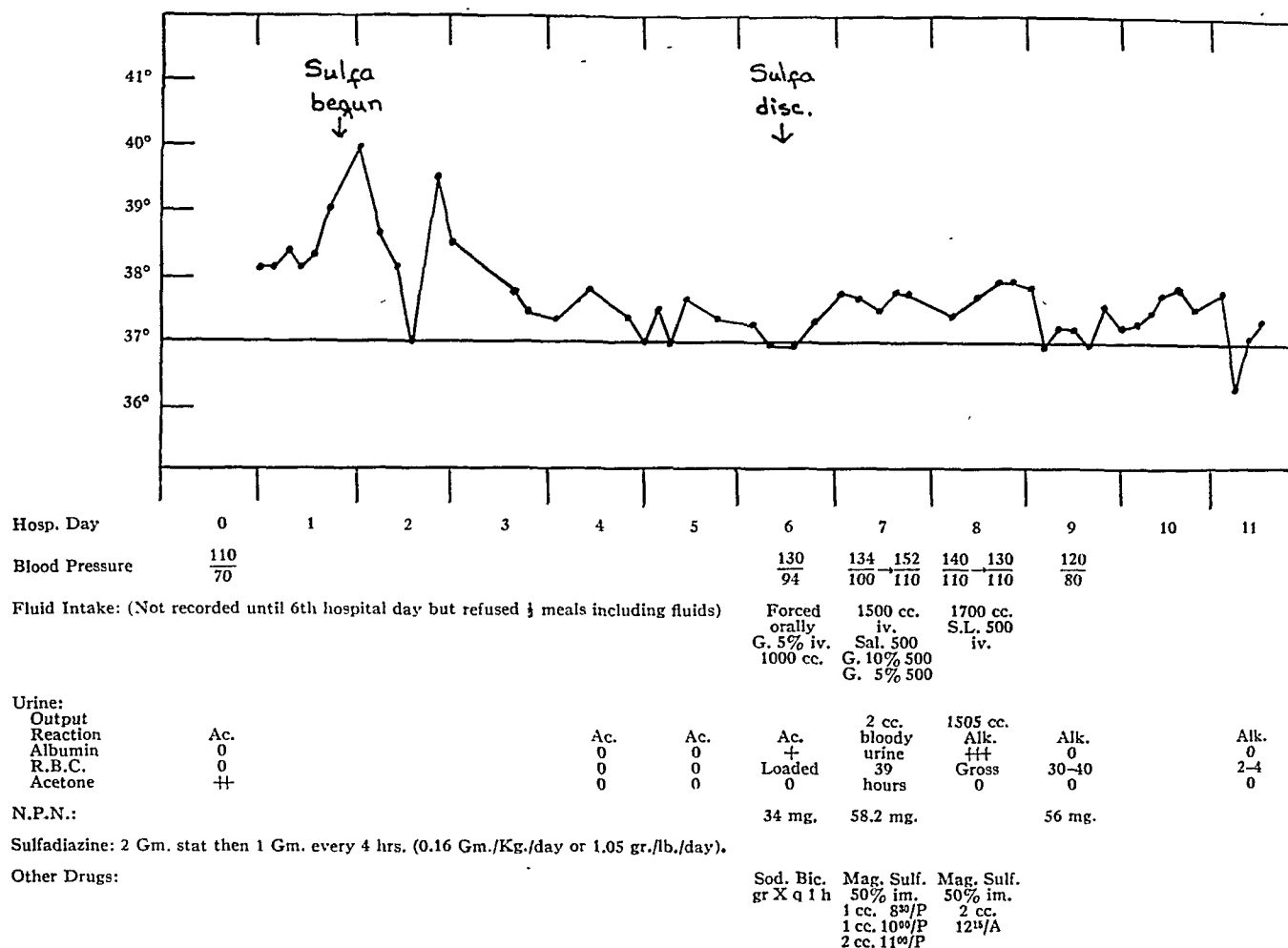
Renal complications such as hematuria, oliguria and anuria comprise over 50 per cent of the reported cases of reaction to sulfonamides. These complications have been of two types: (1) Apparently entirely mechanical with deposition of sulfa crystals, usually of the less soluble acetylated forms, in the tubules, calices, pelves and ureters, causing hematuria from irritation of the renal endothelium, oliguria and finally complete anuria; (2) the so-called "toxic" reaction, in general more dangerous with a higher mortality rate than the mechanical form. Postmortem findings<sup>2</sup> in the latter type consist of widely scattered areas of focal necrosis in practically all the viscera. The kidneys are pale and swollen; the cortical markings indistinct and resemble the findings in nephrosis. Gross obstructions are not found anywhere in the urinary tract. The tubules are primarily affected and show degeneration of a nephrotic character. The lumens of many tubules are dilated and contain cells, casts and blood, some to the degree of complete obstruction.

According to Karsner,<sup>3</sup> toxic causes of focal necrosis include certain chemical poisons and the toxins of parasites and saprophytic organisms. He also states that Auer has shown that it is possible to concentrate reacting substances in anaphylaxis so as to produce necrosis. Whether the toxic renal lesions observed in reactions to sulfonamides are the result of direct toxic

\* Clinic from 'The Babies' and Children's Division, University Hospitals of Cleveland.



FIG. 1. N.C., a 9-year-old white boy, Wt. 36.8 Kg. Admitted February 23, 1946.



action of the sulfa drug or of an acquired sensitivity cannot be determined at present. It is possible that a combination of factors may produce the lesions described.

In the course of one year, from November 1, 1945, to November 1, 1946, four cases of renal complications have occurred in infants and children receiving sulfadiazine therapy while hospitalized at Babies' and Children's Hospital of Cleveland. All of these patients recovered.

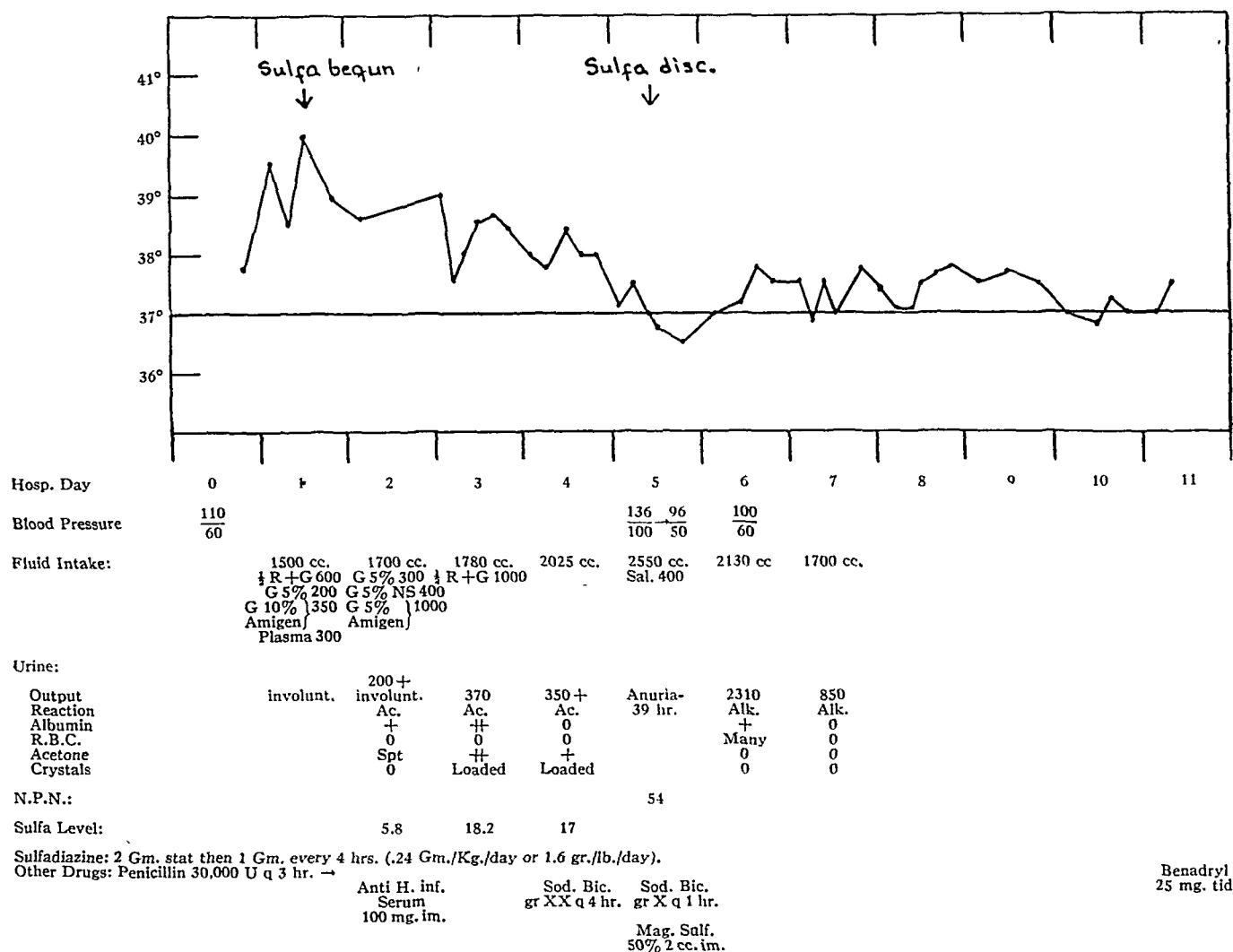
CASE 1. (Fig. 1.) N. C., a nine-year-old white boy, was admitted February 23, 1946, with a 48-hour history of hoarseness, sore throat, malaise, anorexia, fever and vomiting. He had been sent to the hospital because of a generalized convulsion which had lasted for 15 to 20 minutes. On admission, he did not appear seriously ill but had a diffuse pharyngitis.

On the next day the temperature rose to 39.6° C., the postnasal discharge was frankly purulent and the pharynx was much more inflamed. Sulfadiazine was administered (see Chart) and definite improvement in

the clinical condition became evident within 24 hours. Chemotherapy was continued, however, for several days. Gross hematuria with vomiting and pain suggestive of renal colic developed on the sixth hospital day followed by anuria of 39 hours' duration. Sodium bicarbonate, sodium lactate (M/6 solution) and glucose solution were given in amounts indicated on the chart. In an effort to prevent an undue rise in blood pressure, 50 per cent magnesium sulfate was given intramuscularly. A slight edema developed during the period of parenteral fluid administration. As soon as kidney function was re-established, all symptoms of renal insufficiency quickly subsided. The patient was discharged on the eleventh hospital day.

CASE 2. (Fig. 2.) D. D., a seven-year-old white girl, was admitted March 5, 1946, with a 24-hour history of sore throat, dysphagia, fever up to 102° F. with increasing respiratory difficulty. She was apprehensive and appeared seriously ill with moderate respiratory distress. The temperature was 37.6° C. and

FIG. 2. D.D., 7-year-old white girl, Wt. 25.1 Kg. Admitted March 5, 1946.



respirations 34. The pharynx was inflamed, the anterior cervical lymph nodes were enlarged and tender. There was moderate suprasternal, infrasternal and intercostal retraction on inspiration. Penicillin therapy was begun on admission.

Bronchoscopy, done the morning after admission, revealed marked inflammation and edema of the supraglottic structures. The larynx, trachea and bronchi were clear. Swab was obtained from the pharynx for culture and Hemophilus influenza was found in almost pure growth. Sulfadiazine therapy was started along with anti-Hemophilus influenza serum type B after quellung tests had been performed. Respiratory distress, however, became progressively more severe, necessitating a tracheotomy.

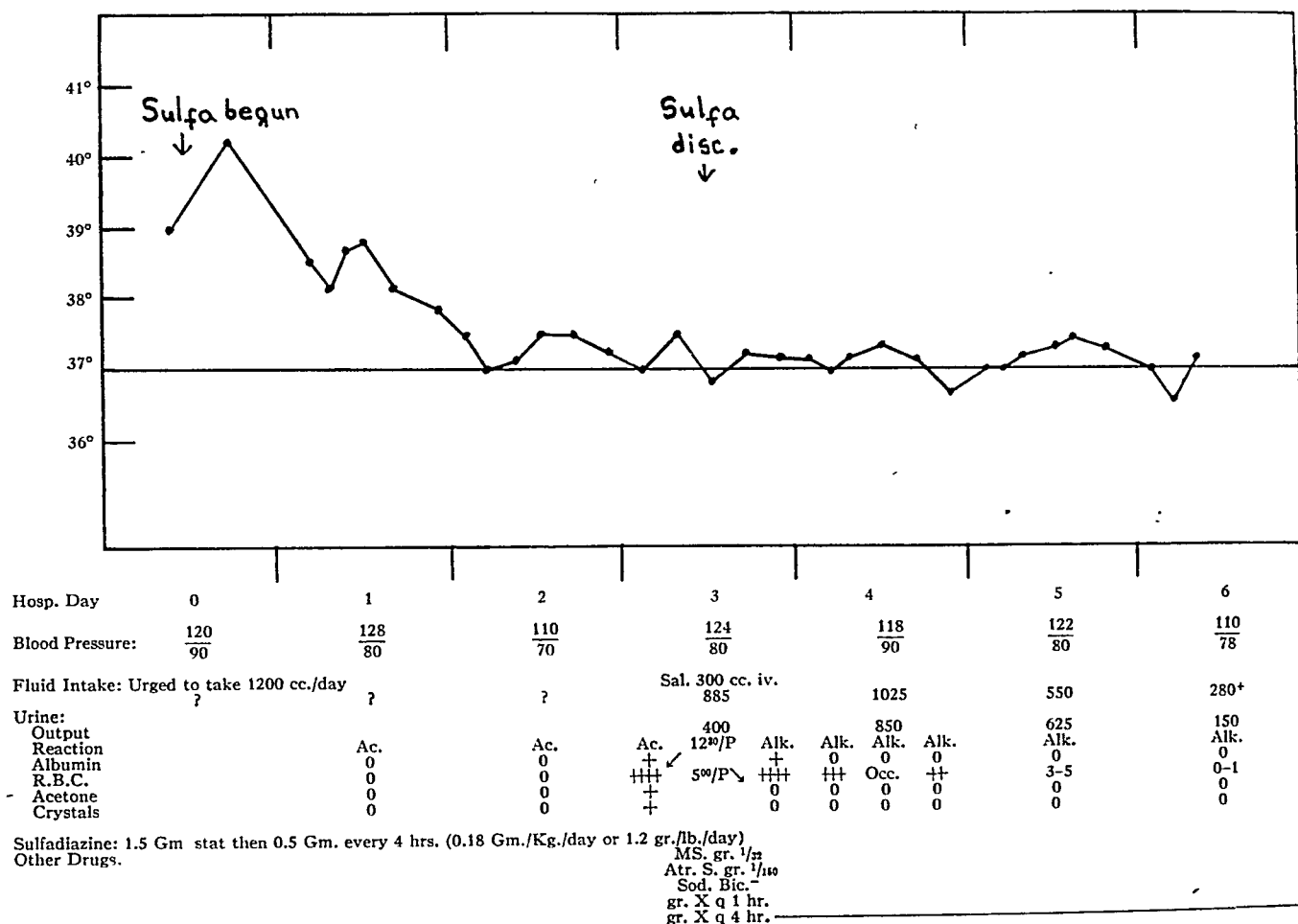
Thereafter, the child's condition improved steadily; sulfadiazine was continued for several days; fluid intake was considered adequate (70 cc. per kilogram) but urinary output was below 500 cc. per day. Uri-

nales revealed acetone, varying from slight trace to two plus. Without any preceding gross or microscopic hematuria, the patient became suddenly anuric on the fifth hospital day with rise in blood pressure and N.P.N. in the blood. Anuria continued for 39 hours. Magnesium sulfate 50 per cent, intramuscularly, and sodium bicarbonate, by mouth, were given as in Case 1. Sixth molar sodium lactate solution was the other parenteral fluid given but fluids were urged by mouth. When renal excretion had again begun, there still was no gross hematuria. The remainder of her course was uneventful except for the development of serum sickness on the eleventh hospital day.

CASE 3. (Fig. 3.) E. Q., a six-year-old white girl admitted March 16, 1946, with a 24-hour history of drowsiness and fever preceded by a slight "cold."

On admission temperature was 39° C., respirations 30, and pulse 118. Examination revealed evidence

FIG. 3. E.Q., 6-year-old white girl, Wt. 16.8 Kg. Admitted March 16, 1946.



only of a nasopharyngitis and a right otitis media with bulging but no perforation of the drum.

Sulfadiazine was given (see Chart) with prompt improvement in symptoms and physical findings. Fluids were ordered to 1,200 cc. per day (70 cc. per kilogram) but no record of the amount actually taken was kept. On the third hospital day, the patient developed a gross hematuria with signs suggestive of renal colic. Sodium bicarbonate orally and sodium lactate 1/6 M solution intravenously were given. The urine became alkaline within 4½ hours but hematuria continued for 24 hours. By the sixth hospital day, the urine was clear grossly and microscopically.

CASE 4. (Fig. 4.) J. S., a 2½-year-old colored boy, was admitted October 5, 1946, with a 24-hour history of congested nose, stomach-ache, listlessness, anorexia and fever. Examination was negative except for an inflamed throat.

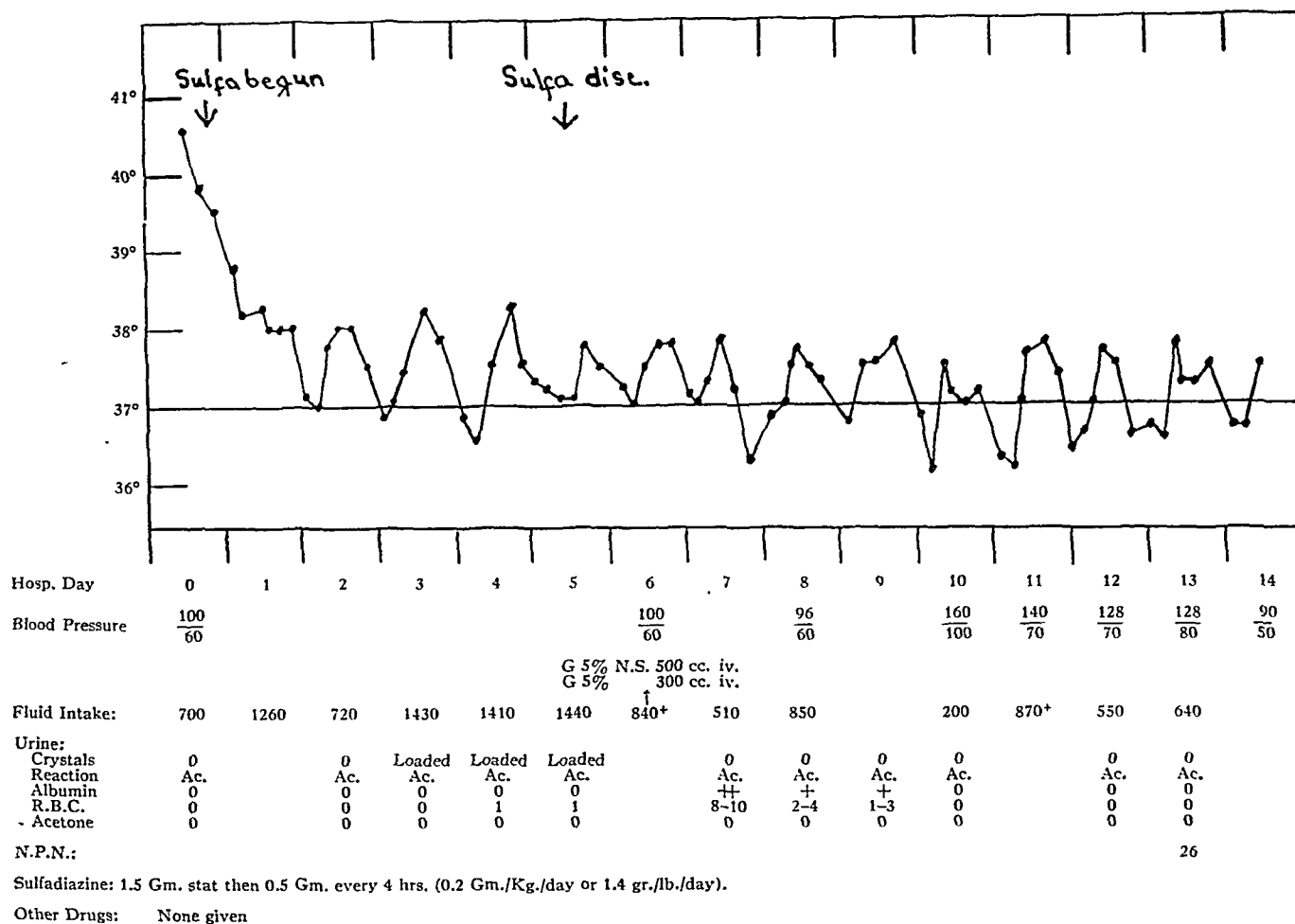
A pharyngeal culture revealed *Hemophilus influenza*, and sulfadiazine was administered, followed by subsidence of the patient's symptoms. Temperature remained normal, but by the fifth hospital day, the

urine contained large numbers of sulfadiazine crystals and medication was discontinued. The following day the boy developed vomiting, albuminuria and hematuria. With cessation of the drug and adequate fluid intake, all symptoms subsided within three days.

Three of these cases (1st, 3rd and 4th) undoubtedly show varying degrees of mechanical renal injury from crystalluria with insufficient fluid intake. The first case presented gross hematuria, costovertebral angle pain and tenderness, vomiting, elevated blood pressure and N.P.N., and anuria with reappearance of gross hematuria as the urinary tract was being cleared; third case presented gross hematuria with costovertebral angle pain and tenderness, but no change in blood pressure and no oliguria or anuria; and the fourth case, the mildest, presented vomiting and microscopic hematuria, no pain or oliguria. The blood pressure became temporarily somewhat elevated after the acute episode had subsided.

The second case evidenced renal insufficiency also probably mechanical but possibly of the "toxic" type. It was unusual in that the anuria appeared without

FIG. 4. J.S., 2½-year-old colored boy, Wt. 14.6 Kg. Admitted October 5, 1946.



any preceding hematuria, gross or microscopic; there was no costovertebral angle pain or tenderness and after the anuric phase the first specimen voided showed only microscopic hematuria which was not present in the next specimen voided one hour later.

Though reactions to sulfonamide drugs are infrequent in infants and children, the question arises as to what steps should be taken to prevent the renal complications. Except for a careful history regarding previous sulfa reaction in the patient to be treated, the toxic reactions probably cannot be prevented, but with attention to the urinary output, the drug can be discontinued when danger signs appear. On the other hand, it should be possible to prevent the mechanical reactions. As has been noted, alkalis were not used in these patients until they were in trouble. The routine use in children of alkalis with sulfa drugs is a debated procedure.

Fox, Jensen and Mudge<sup>4</sup> have demonstrated that increasing the urinary output from 1,000 to 2,000 cc. per day in adults doubles the quantity of sulfadiazine in solution, but raising the urinary pH from 6.5 to

7.5 will permit more than a tenfold increase in solubility. They advocate giving enough sodium bicarbonate to maintain a urinary pH of at least 7.5 (requiring 10 to 20 Gm. per day in the adult). The pH affects the free sulfonamides and the conjugated form, but the latter to a lesser extent.

From reports in the literature, there seems to be no doubt that alkalization increases the solubility of free and conjugated sulfonamides in the urine.

Beyer, Peters, Patch and Russo<sup>5</sup> have shown that alkalis have another action as well as increasing solubility, and that is increasing the renal clearance by interfering with tubular reabsorption, necessitating larger dosage and more frequent administration of sulfa drug to maintain an adequate blood level.

Fink and Smith<sup>1</sup> state that the use of alkali in pediatric patients introduces difficulties in forcing children to take the relatively large amounts of soda needed to render the urine effectively alkaline. In addition, the tendency of alkali medication to induce refusal of oral fluids has been used as an argument against the routine use of alkaline drugs in younger patients.

An interesting suggestion by Lehr, Slobody and Greenberg<sup>6</sup> has recently appeared, advising use of a sulfadiazine-sulfathiazole mixture in an effort to lower the incidence of mechanical renal difficulties. They base their concept as follows: "The precipitation of sulfonamides in the urinary tract is largely dependent upon the solubility and concentration of these compounds in the tubular urine. Solubility studies with sulfonamides revealed that sulfathiazole, sulfadiazine and sulfamerazine, for example, could be dissolved *simultaneously* in the same sample of water or urine to the point of full saturation of each compound when present alone. The concentration of the three drugs in a saturated solution represented, therefore, the sum total of their individual solubilities. It was reasoned that the danger of intrarenal precipitation from the drugs comprising such a mixture should only be as great as if each compound had been administered alone and in the partial dosage contained in the mixture. The validity of this conception was substantiated in animal experimental studies as well as in clinical trials."

The use of sufficient fluid intake to maintain a urinary output of above 200 cc. in infants and above 500 cc. in children<sup>7</sup> is still, in all probability, the most important single factor to be observed in preventing renal reactions. It is difficult for practical purposes, to measure urinary output in infants but as long as the infant voids at least 8 times in 24 hours, we can be reasonably sure that the urinary output is ade-

quate. In older children, actual measurement is not difficult.

## SUMMARY

Four cases of renal complications in children receiving sulfadiazine are described, three apparently representing mechanical kidney obstruction and one possibly a toxic reaction. Reactions in infants and children to the sulfonamide drugs now in wide use are infrequent. Toxic or sensitization reactions probably cannot be forestalled but maintenance of adequate fluid intake should reduce the incidence of renal complications, and treatment with adequate alkalinizing fluids usually results in prompt alleviation of symptoms.

## BIBLIOGRAPHY

1. Fink, H. W., and C. A. Smith: J. Pediat., 28:1, 40 (Jan.) 1946.
2. Lederer, M., and P. Rosenblatt: J. A. M. A., 119:8, 1942.
3. Karsner, H. T.: Human Pathology, ed. 3, Philadelphia, Lippincott, 1932, p. 79.
4. Fox, C. L., Jr., O. J. Jensen, Jr., and G. H. Madge: J. A. M. A., 121:1147, 1945.
5. Beyer, K. H., L. Peters. E. A. Patch, and H. F. Russo: J. Pharm. & Exp. Ther., 82:239, 1944.
6. Lehr, D., L. Slobody, and W. Greenberg: J. Pediat., 29: 3,275 (Sept.) 1946.
7. Poncher, H. G.: Drug Therapy. In Mitchell, A. G., and W. E. Nelson: Textbook of Pediatrics, ed. 4, Philadelphia, Saunders, 1945, p. 195.

## The Michigan and Kansas Plans

Veterans in 32 states, Hawaii and the District of Columbia may obtain free medical treatment for service-incurred disabilities from physicians of their choice under two different plans of the Veterans Administration home-town medical care program, Dr. Paul R. Hawley, VA's chief medical director, has announced.

Both plans enable veterans with service-incurred or service-aggravated ailments, upon approval of their VA medical officers, to go to the local physician of their choice for treatment of that service-connected ailment *only*.

About half the states are operating under the so-called Michigan Plan, the others under the so-called Kansas Plan.

Under the Michigan Plan, a nonprofit organization or corporation sponsored by the state medical society, handles the administrative details for VA, including the payment of co-operating physicians. VA, in turn, pays the organization a lump sum for the professional services rendered, plus a small additional amount for handling the administrative work.

Under the so-called Kansas Plan, all administrative work, including payment of individual doctors, is taken care of by VA and there is no go-between organization.

However, under both plans, state medical organizations serve constantly to see that veterans at all times are getting the best possible medical attention.

# Cases from the Medical Grand Rounds

## MASSACHUSETTS GENERAL HOSPITAL

BOSTON, MASSACHUSETTS

### CASES 1 AND 2

DR. WALTER BAUER: We would like to present two patients with infectious hepatitis. They are both similar in nature and have to date done extremely well. Following a brief clinical demonstration of these two patients, Dr. Tracy Mallory will comment about the histopathology of this disease at its various stages. He has also stated that he would welcome questions from the floor and I am sure that many of you, like myself, have a number of such questions which you would like information on as it pertains to the disease these two people are suffering from.

DR. R. S. SCHAAF: These two patients are Charles B. No. 555171, and William M. No. 554959. Mr. B. said on entry, which was on the 22nd of November, that six days before, having been previously entirely well, having no animal bites, no fever, chills, inoculations, transfusions, or mistreatment of any kind, he began to develop anorexia and feelings of nausea, which continued irregularly until entry. At the time of entry he was reduced to one bowl of soup a day. He had become jaundiced the day before entry and the urine was brown, but his chief complaint on entry was abdominal pain. This was periumbilical and referred to the left upper quadrant. We have not explained that.

The other patient, Mr. M., followed him in two days, with an eight-day story of dullness, malaise, anorexia, a little vomiting, jaundice the day before entry. He had no pain whatever.

On physical examination, Mr. B. had a pulse of 54, blood pressure 104/60. His liver was questionably palpable upon entry but was not felt thereafter. Mr. M. was icteric, a pulse of 54, and blood pressure of 90/50. His liver was never palpable and was not tender. The white count of both of them was 7,000. The differentials were: Mr. B. had 26 polys, 56 lymphocytes, large and small, and 18 mononuclears. Mr. M. had 53 polys, 40 lymphocytes, and 7 mononuclears. Their hospital course has been one of general improvement. The polymorphonuclears in both have shown a rise in the course of about a week to an average now of about 60 to 66 per cent. At the same

time, the van den Bergs have dropped. Prothrombin time has remained constant and four plus bile has been present on all tests of the urine. Urobilinogen initially on both was positive in dilutions of 1:64 and subsequently dropped to 1:16. They both underwent spontaneous diuresis, the younger boy on the 30th of November, or 8 days after admission, and the other on the 3rd of December. They both have been doing fairly well. Mr. M. has been taking about 2,500 calories, whereas Mr. B. has taken about 3,000.

DR. BAUER: Infectious mononucleosis can manifest itself in this manner and should always be considered in the differential diagnosis, particularly in the case of younger individuals. In neither of these patients is there any evidence in favor of this diagnosis. The heterophile agglutination tests were negative and the blood smears did not contain the characteristic mononuclear cells. In neither instance are the clinical findings suggestive of obstructive jaundice of the extrahepatic type or congenital hemolytic anemia.

We believe both patients are suffering from a mild form of infectious hepatitis. Their clinical courses and recorded laboratory tests indicate satisfactory improvement. In neither instance was the spleen palpable. If one makes it a practice to feel for the spleen daily, it is palpable in approximately 70 per cent of the cases.

Dr. Mallory, will you discuss the pathology of infectious hepatitis as you have observed it in its various stages?

DR. TRACY B. MALLORY: It is really rather astonishing, considering what an extremely common disease infectious hepatitis is, how recently have we had any knowledge of its pathology. This is the condition which for 70 years has been known as catarrhal jaundice when it occurs in its mild form and it is the same disease which has been known as idiopathic atrophy of the liver when it occurs in severe form. For a long time the association of the two diseases was not suspected, although many people in England and particularly Scandinavia presented very clear evidence of that association as far back as 1900.

The early ideas of the pathology were derived entirely from the fatal cases, which uniformly show a

massive atrophy of the liver, and it was therefore more or less assumed that mild cases would be as Eppinger suggested, cases of "atrophy of the liver in miniature," a milder degree of the same process. We had a chance in Italy to do a good many biopsies of the liver and I have come to the conclusion that that is not correct; that the process is quite different in the mild and in the fatal cases.

This is the liver of a fatal case, one of the extremely fulminant cases of hepatitis which died within two days of the onset of symptoms so the patient never had time to become jaundiced. The portal areas show extensive mononuclear infiltration, and here is what was once a liver lobule,—nothing is left but the reticulo-endothelial cells. With higher magnification, you see more clearly there is not a liver cell left; within this very brief period of time they have completely autolyzed. Such autolytic necrosis begins at the center of the lobule and spreads peripherally.

In the ordinary benign disease an entirely different picture is seen. There is no dissolution of the liver cells. This slide comes from a man on the first day of jaundice. There is a central vein and there is no loss of liver cells around it. Instead of dissolution of liver cells, one sees a different type of liver cell necrosis. Here is a liver cell which has become much darker than its neighbors. It is beginning to shrink, has drawn in its processes and has started to round up. Here is one that has become completely round and is entirely separated from its neighbors. The nucleus is partly pyknotic. Finally all trace of the nucleus disappears and one is left with a little round red ball, such as one sees here. It is a coagulative type of necrosis rather than the liquefactive type seen in atrophy of liver. These changes are rather like the so-called Councilman bodies which are seen in yellow fever. They are constantly found in the active stages of hepatitis. Cell necrosis of this type was not limited to any particular part of the lobule.

Characteristic also of the biopsy specimens are marked mononuclear infiltration of the portal areas and focal collections of mononuclear phagocytes within the lobules. As early as the first day of the jaundice there is already severe hepatic disease. This is one day of jaundice and here is a section showing five mitotic figures in the high-power field. There has already been marked necrosis of liver cells and very active regeneration has started.

We were able to procure several biopsies before jaundice appeared. In this case, three days before jaundice developed, there is already a well-marked inflammatory infiltration of the portal areas and typical coagulative necrosis of individual liver cells.

Besides being able to secure a number of biopsies in varying stages of the disease, we were interested in many cases which presented the same symptoms as the classical cases but never developed clinical jaundice. This is such a case, biopsied on about the seventh or eighth day of symptoms. His van den Berg showed a rise from 0.5 mg. per cent, which we considered the normal level, to 1.5. Our cases became jaundiced usually at about 2.5. The section shows a moderately severe hepatitis. This man was followed throughout his clinical course and never developed clinical jaundice.

This is the specimen from a man who was followed with almost daily van den Berg tests from the start of his illness through convalescence. He never showed a rise of 0.1 mg. in the serum bilirubin and yet here is a quite frank, although not severe, hepatitis in a patient who had neither clinical nor chemical jaundice.

We also did a lot of biopsies on patients in the convalescent stages of the disease. We saw restitution to normal as early as two weeks after disappearance of jaundice and in patients who were making an apparently uncomplicated recovery we saw persistent hepatitis as late as six weeks after termination of jaundice. There were other patients who had persistent symptoms for weeks or months after jaundice subsided, with or without confirmatory laboratory evidence of hepatic dysfunction; commonly a persistent bromsulphalein retention, less often a positive flocculation test or elevated van den Berg.

DR. BAUER: I wonder if you would be kind enough to comment upon the systemic nature of this disease as seen by the pathologist? What other systems are involved and to what extent, and how frequently? Because I am sure that for a long time we looked upon catarrhal jaundice or infectious hepatitis as being a disease where the causative agent had a specific affinity for hepatic tissue, and we looked upon it, many of us, as a hepatic disease pure and simple. I am sure you people have evidence to the contrary.

DR. MALLORY: There is not much evidence of parenchymal change in organs other than the liver. There is evidence of some changes in the lymphatic system. A slight diffuse enlargement of lymph nodes is very common and, as the two patients that were shown today demonstrated, the patients usually have a quite characteristic blood picture, with a slight leukopenia but a very marked lymphocytosis and sometimes the lymphocytes in the blood are abnormal; in certain smears some cells are found that anyone would mistake for infectious mononucleosis. These cases never show a positive heterophile and I think there is

no other good evidence that they are mononucleosis. The spleen was occasionally slightly enlarged but I have never been very impressed with large spleens. The other changes that have been found in fatal cases, probably all can be interpreted as secondary to liver insufficiency. They are found with other types of atrophy of the liver. Fat deposits develop in the kidneys in acute cases and bile nephrosis in the prolonged ones. In the group of cases following yellow fever vaccine, which Colonel Lucké reported, he found phlegmonous inflammation of the large bowel. That was obviously a very late phenomenon that occurred just a few days before the patient died. Nothing of that sort was seen in the fulminant cases of less than ten days' duration. There are slight central nervous system changes but they appear to be nonspecific.

DR. PAUL D. WHITE: Have you had follow-up biopsies a year or two later?

DR. MALLORY: We are beginning to get a few and the great majority of them are quite negative.

DR. BAUER: How about the instances of encephalomyelitis? In Lucké's series there were 12 or 15 cases, were there not?

DR. MALLORY: Cases of acute hepatitis show very marked central nervous system symptoms. In fact, the entire clinical picture may be predominantly cerebral. There are two cases in the Army files of men who had cerebral explorations for a question of subdural hematoma. On the other hand, the actual histologic findings are entirely nonspecific. They are about what might be seen with uremia. They don't at all suggest actual infection of the brain with virus. It is not a true encephalitis.

DR. BAUER: How about ileitis?

DR. MALLORY: I think Lucké's cases were mostly in the cecum, weren't they?

DR. BAUER: I meant to look it up last night and I couldn't find the reference.

DR. MALLORY: I have forgotten that. I have not got the explanation of that, but in the second series of cases from the Army Museum, which did not follow the yellow fever vaccine, usually running a much more acute course than Lucké's did, that was entirely missing. One hundred and eighty cases did not show it. So I do not think it is characteristic.

DR. F. DENNETTE ADAMS: Were your negative biopsies on the late cases done on cases presumably well, or have you done them on some of the patients who a year or more later are still complaining of weakness, gastro-intestinal complaints, etc.?

DR. MALLORY: We have done several of the latter and the biopsies have been negative. I could not tell you the exact time intervals. Perhaps Dr. Volwiler could say what the longest time interval is.

DR. WADE VOLWILER: We have recently done a series of patients, I think nine in all, that we thought still had prolonged disease. The question was raised whether or not they had developed fibrosis within their liver. There was one of that group who was clinically not very ill, who did not have a palpable liver or spleen, but was icteric. All his laboratory tests of function were very bad. His biopsy, which was a needle biopsy of about an inch and a half long, consisted largely of scar tissue with a picture of atrophy, in which were small bile ductules filled with necrotic liver cells and a very active inflammatory process going on. Two small nodules showed degeneration. Several other patients had abnormal liver function studies and symptoms three to four years after the initial disease; some with relapses, but not all, had evidence in their biopsies of persistence of the inflammatory process. We have had also four biopsies in which all liver function tests were completely normal but the patient still had persistent symptoms of malaise, anorexia, and palpitation always on exertion. All liver function tests were completely normal with the exception of one or two mild changes. These biopsies were completely normal in spite of the fact that the patients were still having symptoms. And I saw in a recent issue of the "Lancet" that the British workers have biopsied a series of men in the Canadian and British Armies who were still having symptoms of various types, whose liver function tests were all normal and all the biopsies were normal.

DR. BAUER: What do your army experiences show, what evidence do you have as to cirrhosis being the end stage of this disease?

DR. MALLORY: In the actual army experience up to the time I left the Army Institute of Pathology, it is not. Personally, I don't believe that. I feel certain I have seen cirrhosis that could be traced back to hepatitis.

DR. BAUER: That was a case where the interval between the initial attack of infectious hepatitis and death was what? Two or three years? Eight years?

DR. MALLORY: Well, we have one case in our own hospital records where the interval was eight years, or ten years, and there was a pair of brothers, one of whom died in the acute stage within ten weeks of onset and the other lived some ten years and died with a typical cirrhosis.

DR. B. M. JACOBSON: Why do some patients show no jaundice? That has always mystified me.

DR. MALLORY: I don't know why any of them show jaundice or do not show it.

DR. BAUER: I think the important thing is that you can have infectious hepatitis *sine* jaundice, as was originally pointed out.



## CASE 3

DR. JAMES KREISLE: This case is one of pneumonia of a lobar type which we are presenting because of the unusual bacteriologic findings. Dr. Dalrymple will present this patient.

DR. WILLARD DALRYMPLE: Mrs. R. No. 554470 is a 32-year-old housewife who entered the hospital on November 20, 1946 with the chief complaint of severe left-sided chest pain for 18 hours. She gave the story that on the evening before entry she had suddenly noticed a severe pain in her left lower chest, which became worse on deep inspiration or on coughing. There was a slight pain on the right side too, but the pain was mostly on the left. During the night she had had several chilly sensations but no frank chills and by morning she had noticed a cough which was mostly dry and hacking.

On admission physical examination revealed dullness and bronchial breathing, mostly over the left lower lobe. Her white count at that time was 16,800. She had a few pneumococci in the sputum. An x-ray was taken of her chest and this showed not only density in the left lower lobe but also in the right middle lobe.

She was very ill and by midnight of that day her temperature was 104°. Her respirations were around 50 and her pulse rate was around 140. These conditions were maintained throughout most of the next day (Nov. 21). Cultures of her sputum were taken on the day of entry and also cultures of her blood. Because of her severe symptoms she was started on penicillin, 24,000 units every two hours, immediately following the taking of cultures. The next day she continued to have pain, there were marked signs of consolidation of the right upper lobe as well as the lower lobe, and at midday *Hemophilus influenzae* were found in the sputum cultures as well as in the blood cultures. Because of this, streptomycin 0.25

Gm. intramuscularly every three hours, was started in the late afternoon (Nov. 21). Also on this day an intercostal block was done by the Anesthesia Service for relief of severe pleuritic pain. Following this, she began to improve and her respirations, temperature, and pulse all subsided over the course of the next few days. She has continued to have pleuritic pain up to the present time. She was wearing a binder up to three days ago; her pain has now subsided to a very occasional bout when she takes a very deep breath or moves around quickly. Her x-rays are over here on the x-ray shelf. They show the improvement which is indicated by the clinical course.

DR. KREISLE: May we see them?

DR. DALRYMPLE: We have those for the 20th (Fig. 1), and the 21st the day after entry (Fig. 2), and here is one which was taken on December 2 (Fig. 3). Her temperature has been normal for the last few days and she is feeling quite well. It would seem to us there is little question but that the etiologic agent of this pneumonia was *Hemophilus influenzae* since both the sputum and blood cultures were taken before any chemotherapy was started and there were no pneumococci cultured from the sputum or the blood.

DR. KREISLE: In addition to that, her pneumonia progressed while she was under treatment with penicillin, and that was the thing that made us suspicious that something was wrong. On the second day the blood culture gave us the clue for the use of another chemical therapeutic agent, streptomycin. This is a very unusual form of pneumonia. In a series of 15,000 cases of lobar pneumonia studied by the U. S. Public Health Service, only 0.06 per cent were due to this organism.

DR. DALRYMPLE: We would like to invite any comment from people who might have had experience with this type of disease. Dr. Pittman, do you have any?

DR. HELEN S. PITTMAN: No, I don't think I have



FIGURE 1.



FIGURE 2.



FIGURE 3.

any. I don't know what Dr. King has in the way of personal experience.

DR. DONALD KING: I don't know the disease. This is not the picture as you got it in the influenza pneumonia of the 1918-19 epidemic. Was she cyanotic when she came in?

DR. KREISLE: Slightly. Her chief trouble was pleuritic pain which was very severe. She had no shaking chills.

DR. KING: In the so-called pneumococcus pneumonia at that time, the cyanosis was very definite: a gray color we have not seen often since. The white counts were very low.

DR. PAUL D. WHITE: Was there supposed to have been a complication of some factor in the influenza cases?

DR. KING: We supposed it was a streptococcus that came in on top of whatever gave the original infection. Most of the people showed that they had streptococci in their chest pus. The influenza bacillus was very seldom actually found in the blood but Dr. Zinsser used to think at that time that it probably was a factor. You remember he had quite a discussion afterwards. I suppose now it must have been a virus with streptococcus on top.

DR. WHITE: Were virus studies done?

DR. KING: No, I don't think so. Blood cultures were taken. We would have picked up some in blood cultures. But the very low white count was the characteristic thing, and the lungs were very wet, and the cyanosis was very characteristic. But actually proved influenza bacillus pneumonia, I don't think we have seen.

DR. PITTMAN: I saw one case when I was a fourth-year student in Baltimore. That is the only one I can remember.

DR. KING: How many did you see, Dr. Adams, when you were on the pneumonia service at the City Hospital?

DR. F. DENNETTE ADAMS: I never saw any. That is one of the reasons I had the patient down here, to see if anybody else had seen one.

DR. WHITE: I wonder if Dr. Mallory has any experience he would like to speak of?

DR. TRACY B. MALLORY: I don't believe I can add anything. You do see a pneumonia due to the influenza bacillus every once in so often. I think we had a fatal one not long ago, if I remember, in this hospital.

DR. KING: That is right. That is one we had a clinicopathologic conference on. But you did not actually find the organism in that case, did you, in the blood?

DR. BEVERLY TOWERY: Not in the blood; in the cultures of the sputum.

DR. MALLORY: That patient had penicillin but not streptomycin.

DR. KING: You found the pure *H. influenzae*. In bronchiectasis that pea-soup sputum that you get in chronic infections is very often a pure culture of *influenzae* but you never thought that was the actual etiologic agent, did you?

DR. DALRYMPLE: Dr. Schatzki had some interesting comments to make, suggesting that it might be a *Hemophilus influenzae* pneumonia. He says, "The appearance of the lesion as well as the progress of the process makes it quite unusual for pneumococcus pneumonia. It is probably consistent with *Hemophilus influenzae* pneumonia. I wonder whether the areas of infarct-like density were caused by areas of hemorrhage?"

DR. ADAMS: It seems hard to believe the patient ever had much hemorrhage without some degree of blood in her sputum, which she did not have.

DR. KREISLE: She had a rusty sputum but not blood. We have been able to find only one similar case reported, that was by Dr. Chester S. Keefer. It was a patient who presented a picture very similar to this only he recovered after the use of sulfapyridine alone.

DR. WHITE: I judge that the pain was very severe?

DR. KREISLE: Yes. Extremely severe and she did not want to breath deeply.

DR. WHITE: What percentage of relief did she get from the intercostal block?

DR. KREISLE: About 75 or 80 per cent. It was very effective.

DR. WHITE: Can you tell us how much use has been made of such anesthesia therapy for chest pain of this sort, Dr. King?

DR. KING: It was used a lot in the Army. That is where they got onto it, I suppose. That is one of the first things they went after in those chest cases.

DR. WHITE: We certainly haven't seen much of it done here.

DR. KING: I think it is well worth having in mind.

DR. WHITE: What did they use?

DR. KING: Novocaine injections.

#### CASE 4

DR. JAMES KREISLE: Dr. Bliss will present this case, an unusual instance of gastro-intestinal disease.

DR. HARRY A. BLISS: Mrs. T. No. 552379 is a 28-year-old, only daughter of French-Canadian parents. She lived in New Hampshire and Massachusetts until about 17. At the age of 12 or 13 when she began to go through puberty, she first experienced gastro-intestinal symptoms. At that time she noticed she

would have watery bowel movements, particularly when she would be about to go out to parties, and at times just after dinner at the parties she would vomit. This condition persisted until she was about 19 years of age without much let-up and in between the bouts of diarrhea she would experience constipation.

At 19 she was working in a shoe factory, again in New Hampshire, doing fancy stitching. At that time she noticed that occasionally she would have to go home from work because of sudden onset of diarrhea and passing of large balls of mucus, about the size of a golf ball. She would feel very weak after these episodes and be forced to go home and rest in bed for about a day.

Shortly after this she became married to a French-Canadian boy and they set up their home in New Hampshire. About five months after they were married, she was two months pregnant at the time, he had to go off to a tuberculosis sanitarium because of sudden onset of pulmonary tuberculosis. At that time he was extremely sick and was on the danger list for about eleven months. He stayed at the sanitarium about two and a half years. Her baby was delivered five years ago and two months later she noticed the onset of diarrhea with some blood streaking in mucus in her stool. This bloody diarrhea persisted for about two years while her husband was in the sanitarium. During this time she was forced to live with her parents, who apparently are quite domineering characters. This bloody diarrhea persisted until she was able to join her husband at the sanitarium in New Hampshire; then the bloody scratchings in the stools stopped, but the mucus persisted.

About six months later she came home from the sanitarium where she was working in the laundry with her husband, and during which time she had been well except for one episode of pyelitis, apparently, during which she had chills, fever and white blood cells in her urine. That lasted about ten days with no recurrence.

When she returned from the sanitarium about two years ago she and her husband again went to live in their own house. About that time she began to notice that her bloody diarrhea became worse and this time she began to pass up to eight or nine bloody bowel movements each day. After about four or five months of this, she changed doctors, he gave her numerous medications and she cleared up. At any rate, the bleeding in her stools stopped though she continued to have diarrhea. Incidentally, she had had an appendectomy because of persistent right lower quadrant pain.

In the past year she has remained well, except for

four or five bouts of watery diarrhea without blood, until about two months ago. Since that time she has had a very severe exacerbation with weight loss, persistent fever, and at first up to 15 or 20 bloody bowel movements each day. Therapy was without avail and at that time it is interesting to note that she was keeping up and not going to bed for fear that her mother would know she was sick. Finally she did collapse and went into the hospital and has felt somewhat better since that time.

While in the hospital she received sulfadiazine, sulfathiazine, several intravenous solutions and also penicillin. Her bowel movements decreased to about four daily, but since she appeared so sick she was sent to this hospital.

Her family history is interesting in that her mother also has inflammatory colitis and has had an abdominal operation.

On admission to the hospital she had a temperature of about 101° and her pulse was 144. She appeared very weak, ill, and flushed. On physical examination her abdomen was very distended but the peristalsis was good. We could not feel her liver or spleen. Her white count was about 10,000 and her red count somewhat decreased. The latter had fallen previously, but has risen following three or four transfusions. Her temperature following admission spiked up to about 105°, by rectum, every day. We decided to put her on sulfadiazine and intravenous fluids because she was vomiting. She reacted very poorly to the intravenous fluids and continued to vomit more. We thought there was some correlation between giving her intravenous fluids and the vomiting. She was also given streptomycin 0.5 Gm. in one-half glass of water to drink morning and night in an effort to sterilize her G.I. tract. The stool cultures, smears and zinc flotations have been negative for pathogens. However, following diazine and streptomycin, she did not seem to get better so she was taken off these and her dietary intake has gone up considerably since that time. Her liver and spleen have become palpable since she has been in the ward and albumen has appeared in her urine. She had a barium enema yesterday. The barium went in very freely and there were no haustrations seen on the sigmoid, descending, or transverse colon. There are numerous small ulcerations on the wall of the bowel. The cecum and terminal ileum were normal so far as we could tell, although there was some fecal material in that region. The evacuation was good. The chest x-ray, incidentally, is normal. Proctoscopy showed a granular hyperemic mucosa without frank ulceration.

DR. F. DENNETTE ADAMS: This patient is both a diagnostic and a therapeutic problem. At first glance

she would appear to have idiopathic ulcerative colitis. However, some doubt concerning this diagnosis is introduced by the fact that although she has improved somewhat since admission, she is still running a high fever which at the moment seems out of proportion to the rest of the picture. With this much fever persisting in spite of good medical treatment, one would expect a much more fulminating type of the disease than seems to be the case here. We have considered the possibility of tuberculosis. In this disease, of course, involvement of the intestine would be greatest in or near the cecum. With the enlargement of the liver and spleen one would have to think in terms of miliary tuberculosis, in spite of negative x-ray films of her lungs. In miliary tuberculosis x-ray changes in the lungs often appear late. There is a history of intimate exposure to open tuberculosis. We have not known until this morning, because of fear of having barium studies of the colon any earlier, that her cecum is not involved. This information plus the appearance of the mucous membrane on proctoscopic examination excludes tuberculosis. One should always consider amoebiasis in any case of this kind. It seems unlikely here, but a therapeutic trial of emetine might be wise.

The large liver and spleen complicate the problem. They may be enlarged in chronic ulcerative colitis but usually only in cases with severe malnutrition, except in the presence of amyloid disease. A congo red test performed this morning is normal, making amyloid disease unlikely.

What should we do next? We have tried sulfa drugs and oral streptomycin without any appreciable improvement. My own opinion is that we should first exclude amoebiasis by giving a six- to eight-day course of emetine. If, as we anticipate, no improvement results, then we must decide whether medical treatment has had a sufficient trial or whether we should entertain the thought of surgical intervention. This woman has been chronically sick for seven years and has had several acute exacerbations. She is losing a lot of blood, necessitating repeated transfusions. Thus far she cannot be regarded as a therapeutic triumph. How much longer should we let her struggle on with sepsis, uncontrollable loss of blood, the danger of perforation, of involvement of the ileum, and of developing amyloid disease if she does not already have the latter? Should we not seriously consider ileostomy if her anti-amoebic treatment proves useless, and anticipate that months from now her colon should be removed?

I have asked Dr. Perry Culver to give us his views.

DR. PERRY CULVER: Do you want to see the patient first?

DR. ADAMS: This patient apparently is a lot better than when she came in. The edge of the spleen is palpable. Her abdomen is a little distended but not badly at the present time. The blood counts are all normal. She had some anemia, but that has been corrected.

DR. CULVER: There are several interesting observations in this case. One is the apparent picture of good nutrition in spite of a long history of small intake and vomiting. The second thing is the absence of any of the usual complications of colitis, such as clubbing of the fingers or toes, sore tongue, cracked lips, signs of malnutrition, and secondary infections of the perianal regions. She is lacking in all these. She has none of the usual deficiency signs we often see.

There is time to make a few brief points about ulcerative colitis. One is that I have not seen too much of it; but Dr. Jones has seen a great deal and he emphasizes over and over again that every case is a law unto itself. This case differs from many of the cases we see in having a prolonged spiking fever, yet there have been a number of cases with protracted fever similar to hers.

As Dr. Adams points out, there is a question of diagnosis. I agree with him that amoebiasis probably should be ruled out by therapeutic test with emetine hydrochloride, 25 mg. subcutaneously twice a day for seven days. If there is not a marked response in 4-5 days the emetine therapy should be discontinued. Certainly she does not present the picture of amoebic dysentery; but Dr. Jones teaches that with prolonged fever you have to give the patient the benefit of doubt. The question of tuberculosis has been raised here. The proctoscopy gives evidence against it. If she had tuberculous involvement of the bowel to this extent she should be sicker than she is. Also she has a negative tuberculin test, and while that does not rule it out, it is another bit of evidence against it, in spite of the history of contact with cases of active tuberculosis.

Then we come to the problem of treatment. That is the big one here. Because of such extensive disease in the colon she will have to be prepared for ileostomy and subsequent colectomy at the proper time. You cannot wait until these people are in an exhausted state. Ileostomies do not work well when patients are in that condition. They do not save life. On the other hand, you cannot do it too early in the course of ulcerative colitis because the patients will not accept it mentally. This patient so far has been resistant to the idea of an ileostomy. She has pointed out several times that she will not have one. She has not been troubled by her diarrhea severely enough to decide that an ileostomy is preferable to diarrhea. Since the outstanding characteristic of her clinical pic-

ture has been fever with an invasive type of ulcerative colitis, rather than a diarrheal type, she does not realize how seriously ill she is. If she had a lot of diarrhea and were malnourished, she would probably be more ready to accept an ileostomy. This mental attitude is a big obstacle in treating her. I think without any doubt that a medical regime is not going to achieve any satisfactory result and that she is going to come to an ileostomy and probably a colectomy. In the meantime we have to set a definite time limit to medical treatment. In these cases you have to say, "Now, in exactly one or two months we are going to review this case and decide at that point whether she is improved enough to go on with a medical regime or whether an ileostomy must be done." I think that is the thing to do here.

Her failure to respond to chemotherapy is not unusual. In fact, that is fairly characteristic. Some of the early acute cases respond with fairly dramatic results to sulfadiazine or sulfapyridine before they have had years and years of infection, but she has gone so far I do not believe she is going to respond. Penicillin has never been of much value in ulcerative colitis. Streptomycin has been tried in a few cases and has not given any striking benefit. We tried streptomycin by mouth. It "sterilized" her intestinal tract, but that did not reduce her fever. Enlargement of her liver and spleen has caused some comment. With so much infection draining into the portal system, it is a wonder that we do not see much more hepatomegaly and splenomegaly.

Maintenance of nutrition is one of the important aspects of treatment. Whenever there is much diarrhea, the customary route of alimentation is by intravenous feeding in the hope that it will put the bowel at rest. This patient reacted adversely to intravenous fluids by vomiting with increased severity. When intravenous therapy was discontinued, her spirits improved. She stopped vomiting and her oral intake exceeded 2,500 calories a day, enough to maintain nutrition. Since food by mouth did not increase her bowel activity or produce abdominal cramps, I think it is preferable here.

To summarize: The program here should be to get her in the best nutritional shape possible, put a certain time limit on medical treatment, sell her on the idea of an ileostomy, then go ahead and do it.

#### CASE 5

DR. ROBERT SMITH: Mrs. S. No. 540626 is 32 years of age, a French-Canadian housewife, who was shown here in Grand Rounds on August 15th of this year. On that admission she came to the hospital in acute Addisonian crisis and she was shown last time as an

example of a very severe Addisonian crisis. We have on the board some of the findings at that time. She had a temperature of 100°; pulse 160; respiration 10; blood pressure 70/30; her blood sodium was 128.1 m.eq./l.; chloride 82 m.eq./l.; potassium 4.7 m.eq./l.; blood sugar 87 mg. per cent; CO<sub>2</sub> 18.9 m.eq./l.

She was treated very drastically at that point and, in fact, at one time there were five of us in line waiting to put our syringes into her. By four o'clock that same afternoon the blood pressure was 110/54. She was very paranoid, very much confused, and she did not become oriented for three days. It was not until the second of August that she knew what was going on.

Her course in the hospital after that was relatively uneventful. On the 15th of August she received DOCA (desoxycorticosterone acetate) pellets, three pellets of 75 mg. each, and was discharged. She was seen September 28th in the Outpatient Department and was found to be in excellent shape, far better in fact than when she was discharged. She was seen again on the 8th of November in the Outpatient Department and was found to be in excellent shape. She stayed in Boston that night (she lives in Maine) and the following day as she was shopping she developed a substernal pain which by evening had become quite annoying. During the afternoon she vomited a few times, so she walked to the Emergency Ward where she was found to be somewhat drowsy and quite restless, with nausea and a story of having vomited. She did not vomit for us.

On examination she was found to have a pulse of 100; blood pressure 104/68. Because of the substernal pain she had an x-ray taken, which showed a very large heart compatible with a pericardial effusion. By the time she had gotten back from x-ray her pulse was 102, blood pressure 86/40. We called a chemist, who was very disgusted with us because the tests made at that time were very normal; sodium 141 m.eq./l.; chloride 102 m.eq./l.; blood sugar 119 mg. per cent and CO<sub>2</sub> 26.5 m.eq./l.

So, our immediate problem was: Here was a patient with normal blood chemistry findings, restlessness, vomiting, suggesting Addisonian difficulty, and with a low blood pressure and a large heart. It wasn't until about two hours later than we were able on listening to the chest to hear a pericardial friction rub. Her blood pressure stayed relatively low during that night and the following day, and at two o'clock Sunday (she came in Saturday night) her pericardium was tapped because she had a pulse of 126 and a blood pressure of 60/40. Two hundred cubic centimeters were removed on this occasion and the response was not dramatic. She was at the same time given adrenal

cortical extract and DOCA. Blood samples were drawn and showed sodium 137 m.eq./l.; chloride 98 m.eq./l.; and CO<sub>2</sub> 19 m.eq./l. It was not until six o'clock that her blood pressure got up to 105/55.

DR. JOSEPH C. AUB: Are you sure she got DOCA?

DR. SMITH: She got a small amount of DOCA.

DR. JAMES KREISLE: Five milligrams at that point. She received three milligrams and 30 cc. adrenal cortical extract on the night of her admission.

DR. SMITH: She got five milligrams and she had 60 cc. of adrenal cortical extract, the first dose intravenously. Then there was one episode on the 17th of November when she had a similar period where her blood pressure went down, her pulse became more rapid, not much, and again she was tapped. This time, I believe, 350 cc. of fluid were taken off, and again her response was very slow. She was put on adrenal cortical extract and her blood pressure gradually came up. On one occasion recently, because she was so sore from the injection of extract, we stopped giving it, and her blood pressure over the next three or four hours went down to about 80, I believe.

DR. AUB: We can show the patient now. This patient shows various things that are of considerable interest. She has very marked pigmentation. With her bright blue eyes it is an interesting combination. She has no hair under her axillae. She has a rather large liver, down about three or four centimeters, rather tender, and after she had been in three days she had a palpable spleen, which is down about two centimeters and can be felt easily. She has fluid in her abdomen and this recurring fluid in her pericardium. She looks progressively better since she came in. She has had an enormous amount of adrenal cortical extract and a little DOCA on entry.

DR. JAMES H. MEANS: Does she have peripheral edema?

DR. SMITH: Never has had.

DR. WALTER BAUER: What is her venous pressure?

DR. SMITH: Her venous pressure has never been measured directly, but venous distention has been mild.

DR. FULLER ALBRIGHT: What is the pellet situation?

DR. SMITH: She had three pellets in August, 75 mg. each.

DR. ALBRIGHT: No testosterone?

DR. AUB: No testosterone.

DR. CHESTER M. JONES: Has there been any elevation of temperature?

DR. AUB: Her temperature has gone up as high as 102°. Now I thought I made a brilliant diagnosis. I thought she had hemochromatosis. That was not correct. She had only melanin on her skin.

DR. BAUER: Did the enlargement of the liver and

spleen all appear for the first time subsequent to the onset of the pericarditis?

DR. AUB: It is difficult to account for those physical findings on that basis. That is the reason I could not understand the enlargement of the spleen. The enlargement of the liver you could say is due to the pericardial infection; but the spleen—I don't see how you can have enough congestion to produce enlargement of the liver and spleen without having neck vein distention.

DR. BAUER: I thought she had edema of the face today, but I may be wrong. Maybe she doesn't have.

DR. AUB: We haven't thought so. She had a little free fluid in her abdomen. I thought the diagnosis was tuberculosis. I don't know what other diagnosis you could make.

DR. MEANS: If she has tuberculosis do you think the liver could be tuberculous, or the spleen? Or do you think they could both be due to amyloid?

DR. AUB: I thought she might have either amyloid or hemochromatosis. She might have amyloid in her liver as a result of tuberculosis. Dr. Means forgets he told me the other day that tuberculosis of the liver was so rare that I ought never to make the diagnosis.

DR. MEANS: Dr. Chester Jones told me that. (Laughter.) I missed the diagnosis.

DR. PAUL D. WHITE: I would like to make the diagnosis of polyserositis.

DR. AUB: I should think so too. It could not be amyloid or anything like that.

DR. KREISLE: The pericardial fluid was slightly cloudy, yellow, with specific gravity of 1.016; 12,000 leukocytes, 92 per cent of which were polys. The culture was negative and no bacteria were seen on microscopic examination.

DR. JONES: This sounds like an exudative process rather than a transudate. Do you want to tap to find out what kind of a liver it is?

DR. AUB: You mean by liver puncture?

DR. JONES: Yes.

DR. AUB: I always hate to object to anything like that but I don't think she is in any condition to have it now. She is better now; give her a few more days.

We have here the x-rays. Here is a small heart the first time she came in. This is her heart now. There is no question but that she has a large pericardial effusion. We don't know the size of her heart when she came in and therefore it was a little risky, considering the amount of fluid here, so we abstained from giving DOCA and gave only the adrenal cortical extract, which she has had in large quantities. Whether she ruptured a tubercular node into the pericardium and whether she has tuberculous peritonitis, I cannot be sure.

# BOOK REVIEWS . . .

**PENICILLIN, ITS PRACTICAL APPLICATION.** Edited by Sir Alexander Fleming. 380 pp. with 59 illus. Philadelphia, Blakiston, 1946. \$7.00.

This book was edited by Sir Alexander Fleming, winner of the 1944 Nobel Prize in Medicine for the discovery of penicillin. He states at the outset that he is not a clinician, hence he has enlisted 28 authors to contribute to the 27 chapters. The authors are British and the British experience is primarily represented here with no attempt at a comprehensive review of the literature. The bibliography is quite limited but the book is readable, didactic, fairly comprehensive yet not greatly detailed. Parts are well illustrated with photographs and charts.

Chapters have been written on the history, production, chemistry, pharmacy, pharmacology, methods of assay, preparations, methods and routes of administration of penicillin. There are chapters on specific infections, on the use of penicillin in surgery, obstetrics, gynecology, dermatology, otolaryngology, dental infections and in animal infections.

The authors have placed the emphasis entirely on the practical aspects of penicillin therapy. They have devoted considerable space to treatment regimes, dosages and methods and routes of administration. The indications for treatment and, where figures are available, the results of treatment are discussed. Since the chapters are based mainly on the experience of each individual contributor much of their data is sparse. Few chapters contain series of cases which are sufficiently large to warrant final evaluation in any specific condition. Notable exceptions are in the case of certain army experiences such as the treatment of wounds and gas gangrene.

The opinions and conclusions are drawn at a time when the evaluation of penicillin is still in an early stage. Many of the ideas that are expressed have already undergone revision and more changes and additions are taking place constantly. Nevertheless, this book has a useful place in acquainting students and physicians with the uses, limitations and background of this antibiotic which has rapidly assumed one of the most prominent places in our modern therapeutic armamentarium.

E. ORY.

**TREPONEMATOSIS.** By Ellis H. Hudson, M.D. 122 pages. New York, Oxford University Press, 1946. \$2.50.

This book is a reprint from Oxford Loose-Leaf Medicine. It sets forth the author's idea that there is only one treponema, namely, the *Treponema pallidum*, which is pathogenic to man.

The biologic characteristics of the organism are described. There follows a very complete historical review of syphilis as a disease. Such a review obviously presents all the pros and cons of the viewpoints of the Eurasian and of the American origins of the disease. This is a most interesting section of the book to anyone interested in this disease.

The remainder of the book is given over to the author's thesis that treponematoses are a universally distributed disease, in an acute and in a chronic form. The nonvenereal and venereal forms of the disease bear direct relationship to epidemiologic factors of climate and sanitation. Thus in the tropics with much moisture and warmth and with uncleanness in primitive peoples, treponematoses appear as yaws or bejel, a childhood disease, passed from person to person as nonvenereal treponematoses. In the temperate zones and with greater cleanliness only two areas remain with the attributes (moisture, warmth and often uncleanness) needed for transmission, the mucous membranes and the genitalia—thus venereal treponematoses or syphilis. Hudson points out that transitional forms of treponematoses may be seen. In times of poorer socio-economic conditions as after wars and famines, syphilis has changed from a venereally transmitted disease to one of nonvenereal nature, transmitted as such from person to person in all age groups at times in an almost epidemic fashion. This has been encountered in Russian peasant groups, in Scotland, Ireland, Norway, Bosnia and Herzegovina, Greece, Crimea, Turkey, etc.

This small volume makes interesting reading for the physician interested in syphilis and the arguments which have raged over its origin and the unitarianism of treponematoses.

R. H. K.

# CASE REPORT . . .

## Periarteritis Nodosa\*

HORACE PETTIT, M.D.

PHILADELPHIA, PENNSYLVANIA

*This case report shows the extent to which clinical findings may develop in periarteritis nodosa, and indicates the difficulties of diagnosis.*

Eighty years after periarteritis nodosa<sup>1</sup> was first described, the etiology remains undetermined and the diagnosis during life remains difficult. Recognition of periarteritis nodosa follows microscopic examination of the tissues at biopsy or autopsy, usually the latter. It is important, therefore, that the clinician think of periarteritis nodosa in diagnostic problems involving signs and symptoms listed by Harris, Lynch and O'Hare.<sup>2</sup> The case presented here exhibited 13 of the first 16 and 5 of the remaining 15 of the characteristics noted by these authors. This is 58 per cent of the entire list. However, since the most important comprise the first 16, it is fair to say that 81 per cent of the signs and symptoms were shown by this patient. The list is presented in the discussion, with those characteristics displayed by the patient in italics.

CASE. S. E. B., a housewife aged 63, was admitted to the Hospital of the University of Pennsylvania in September complaining of painful hands and feet. She had first noticed stiffness of her hands and feet eight years previously. For a year following tonsillectomy seven years before, she had complete relief. However, each winter since then she had exacerbations of stiffness. During the summer just before admission the little finger of her right hand became tender, swollen and stiff. This process spread to the other fingers of her right hand, to those of her left hand, to both legs, ankles and feet. She had difficulty moving parts of her extremities which had been in one position for a while. She described her pain as "like a toothache." There was never redness or heat.

Her weight loss had been 20 lb. in the previous six months. In the same period, she had numbness of her great toes. She suffered dyspnea on exertion and decreased exercise tolerance for one year, along with

a persistent cough with morning sputum. Ankle edema occurred. Anorexia had become constant. A few tarry stools had been noticed by the patient. She passed a large quantity of urine twice every night.

The only childhood diseases she had had were measles and mumps. At the age of 28 she had severe whooping cough. From the ages of 38 through 43 she had pleurisy each winter; the last attack following pneumonia. Her uterus, ovaries and appendix were removed in her 49th year. Neither asthma nor hay fever had afflicted her.

The family and social history were noncontributory.

Physical examination showed a slight emaciated woman with gray hair. She appeared older than her age. She was alert intelligent co-operative and not in distress.

On admission, her temperature was 99.0° F.; pulse 86, respiration 20, blood pressure 120/70 on the right, 130/80 on the left, reclining.

The skin was wrinkled, showing loss of subcutaneous tissue. There were several yellow raised plaques from 3 to 10 mm. in diameter on her abdomen.

The dorsa of the hands and wrists were of a light bronze color. The digits were symmetrically swollen: more at the first phalangeal joints and tapering to the tips. The fingers were mottled irregularly pink and white with cyanotic nail beds. Heberden's nodes were on the ungual phalanges.

The nails showed longitudinal striae. There was moderate contraction of the right little finger, slight of the left. The hands were cool and moist. Phalangeal movements were impaired. Pressure over the joints gave moderate tenderness.

From toes to knees bilaterally there were areas of purple mottling, pitting edema and tenderness. The dorsalis pedis pulses were palpable; the posterior tibial pulses could not be felt. Ophthalmoscopic examination of the eye grounds showed no abnormalities other than slight tortuosity of the fine arteries.

There were three keratotic raised nontender hard papules from 2 to 3 mm. in diameter on the right external ear. Both ear drums were thickened. The temporal arteries showed moderate tortuosity.

\* From the Department of Medicine, Medical School of the University of Pennsylvania, Philadelphia, Pa.



Around the mouth were superficial vertical fissures. The gums were atrophic and the mucosa pale. The dorsum of the tongue showed atrophy of the papillae and moderate injection.

Diminished expansion of the lung was found bilaterally. Bronchovesicular breath sounds and many crepitant inspiratory râles were heard at the left base, few at the right.

The heart was enlarged to percussion. Soft pulmonary and mitral systolic murmurs were heard.

The abdominal wall was relaxed, retracted, with thin panniculus. Peristalsis was visible.

Vaginal examination showed atrophic external genitalia.

Rectal examination showed a few hemorrhoidal tags, poor sphincter tone, and tenderness of the left cervicosacral ligaments.

The peripheral nerve reflexes were normal. Sense of position was intact.

Laboratory Studies. RBC 4,000,000. Hb. 77 per cent. WBC 10,000. Differential: polymorphonuclear leukocytes 62 per cent, lymphocytes 28 per cent, monocytes 10 per cent, eosinophiles 0. Platelets 356,000.

Blood Chemistry: Calcium 10.8 mg. per cent. Phosphates 3.6 mg. per cent. Cholesterol 240 mg. per cent. Protein 6.4 Gm. Uric acid 3.1 mg. per cent. Kolmer & Kahn negative.

BMR — 4 per cent. Occult blood in stools positive on two occasions. No ova or parasites.

Urine: Sp. gr. range 1.011 to 1.023. No albumin, no sugar. Hyaline casts were found in one of five urines, 1 to 2 per h.p.f.

Roentgen Examinations. Joints: Negative for arthritis. Needle in soft tissues of distal phalanx of right great toe:

Chest: Emphysema and calcification in both upper lobes (not an active process).

Barium Enema: First examination, "possible carcinoma in transverse colon"; second and third examinations, "normal colon."

Lumbosacral Spine: Hypertrophic changes and possible old fracture at T 11.

Gastro-intestinal Series: Negative.

Vasodilatation Test. Skin temperature of toes rose to low normal level after heat to arms.

### COURSE

The edema and pain gradually diminished with bed rest and high vitamin intake. Consultants in dermatology, arthritis and peripheral vascular disease agreed that there was some disease in the group including scleroderma, acrosclerosis, Reynaud's disease, and dermatomyositis.

The patient was discharged, improved, after 17 days on the ward. She was asked to return to the ward in six weeks for further study and to attend the Medical Outpatient Clinic in the interval.

Four weeks after discharge she was seen in the Outpatient Clinic complaining of increasing pain in her hands, legs and feet. Both lower extremities were extremely mottled and tender. Her hands were reddened and swollen.

These symptoms and signs subsided spontaneously, but eight weeks later they returned with increased intensity and she was re-admitted to the ward.

On this second admission physical examination differed only in that her blood pressure had risen to 145/90, her temperature to 101.0° F., pulse to 100 and respirations to 24; the peripheral vessels had become

TABLE I.

	GROSS ANATOMIC	HISTOLOGIC
Serous cavities:	Chronic fibrous and caseous pleurisy, bilateral; left hydrothorax; localized fibrous adhesions of peritoneum.	
Heart:	Normal	Myocardial scarring
Lungs:	Emphysema; edema; right bronchopneumonia; left lower lobe atelectasis; right upper lobe fibrocaceous localized tuberculosis.	Bilateral bronchopneumonia and edema; emphysema.
Liver:	Normal	Periarteritis nodosa; passive congestion.
Pancreas:	Normal	Periarteritis nodosa (active and healed)
Spleen:	Normal	Periarteritis nodosa
Adrenals:	Normal	Periarteritis nodosa
Kidneys:	Nephrosclerosis (??) Small	Periarteritis nodosa
Bladder:	Acute cystitis	Acute cystitis; periarteritis nodosa.
Genitalia:	Old hysterectomy	
Lymph nodes:	Normal	Normal
Stomach:	Superficial ulceration	Superficial erosion; periarteritis nodosa.
Sigmoid:	Multiple diverticula	
Vertebrae:		Myeloid hyperplasia; periarteritis nodosa (in periosteal tissue)
Skin:	Scleroderma, left hand	(Hand) hyperkeratosis; periarteritis nodosa.
General:	Emaciation; edema of ankles.	

markedly sclerosed and slightly beaded; the plantar reflexes were absent; there was almost complete anesthesia of the backs of her hands.

Evidence of impaired renal function was demonstrated for the first time. Urinalysis showed a specific gravity range of 1.018 to 1.002. Albumin was constantly present from barely perceptible to moderate amounts. Hyaline casts and leukocytes appeared in increased numbers. Culture revealed large numbers of *B. pyocyaneus* two weeks after admission. Renal function test was 25 per cent of normal.

Blood studies showed constantly decreasing numbers of erythrocytes which dropped to 3,500,000. Leukocytosis reached 62,000 with a differential count of polymorphs 67 per cent, lymphocytes 25 per cent, monocytes 5 per cent, eosinophiles 2 per cent, basophiles 0, myelocytes 1 per cent. The cells showed many toxic granules. Two samples of serum gave titers of 1:200 with typhoid H antigen; a third sample was negative. Blood culture and stool culture were negative for *E. typhosis*.

During the fourth week of her second admission she developed bronchopneumonia and died in three days.

The autopsy was performed in the Department of Pathology. The gross and microscopic findings are tabulated below. The diagnosis of periarteritis nodosa was not made until the tissues were examined under the microscope.

## DISCUSSION

The list of symptoms and signs compiled by Harris, Lynch and O'Hare<sup>2</sup> from their study of 101 cases of periarteritis nodosa (Table II) is arranged in order of prevalence. Those which were found in the present case are in italics. The last three are added.

*Fever.* First admission: Range 99.6° F. to 97.4° F., fluctuating between these limits almost daily.

Second admission: Range 101.2° F. to 96.2° F., being in the higher range without touching normal from the 13th to the 16th day. Subsequently, the range was narrower, never rising above 99.2° F. to the end.

Her pulse was always rapid while she was under our observation, reaching 134 two days before she died. The range was from 76 to 134, usually around 104.

*Leukocytosis.* First admission: 10,000–11,000–7,300.

Second admission: 17,250–23,000–62,000. Polymorphonuclear leukocytes predominated. On the last count, however, the monocytes rose to 19 per cent. There were consistently from 5 to 10 per cent on both admissions. Eosinophiles never rose above 3 per cent.

TABLE II

SYMPTOM OR SIGN	NUMBER OF PATIENTS
<i>Fever</i>	80
<i>Leukocytosis</i>	70
<i>Albuminuria</i>	65
<i>Hypertension</i>	64
<i>Rapid onset</i>	58
<i>Abdominal pain</i>	57
<i>Edema</i>	52
<i>Loss of weight</i>	48
<i>Neuritis</i>	48
<i>Hematuria</i>	47
<i>Dyspnea</i>	41
<i>Weakness</i>	41
<i>Emaciation</i>	36
<i>Cough</i>	36
<i>Vomiting</i>	31
<i>Sensory involvement</i>	31
<i>Headache</i>	29
<i>Arthritis</i>	27
<i>Atrophy</i>	25
<i>Visual disturbances</i>	23
<i>Purpura</i>	22
<i>Cyanosis</i>	21
<i>Eosinophilia</i>	19
<i>Nausea</i>	17
<i>Nodules</i>	16
<i>Pain in the chest</i>	16
<i>History of allergy</i>	15
<i>Convulsions</i>	15
<i>Icterus</i>	12
<i>Vertigo</i>	8
<i>Positive serological reaction</i>	8
<i>Occult blood in stools</i>	—
<i>Low normal vasodilatation test</i>	—
<i>Scleroderma</i>	—

*Albuminuria.* First admission: Not found.

Second admission: From barely perceptible to moderate amount, mostly the latter.

*Hypertension.* First admission: 100/60–130/80.

Second admission: 185/90–150/110–120/80.

*Edema.* Peripheral edema became a sign three months before her first admission. This was of greater degree at night than in the morning and was limited to the hands, lower legs, feet and ankles; it was a constant finding.

*Loss of weight.* The patient lost 20 lb. in three months.

*Neuritis.* The chief complaints were pains in the hands, lower legs and feet. These pains were severe and almost constant for five years. There was no tenderness along the course of the larger peripheral nerves. There was almost complete anesthesia over the back of the hands.

*Hematuria.* Blood was found in two urine specimens during the second admission.

*Dyspnea.* Breathing caused her pain during the last three days of life. Respirations ranged in rate

from 20 to 28 through both admissions; toward the end the rate reached 42 once.

**Weakness.** Weakness was most troublesome to the patient. It ranked next to pain. Weakness increased a week before her second admission and progressed to the end.

**Emaciation.** Her emaciated appearance on the first visit to the Medical Outpatient Clinic was one of the chief reasons for admitting her to the ward for study.

**Cough.** Persistent morning cough productive of a slight amount of whitish sputum.

**Sensory involvement.** Numbness of both great toes since three months before first admission. Numbness of hands and shooting pains in hands and feet were present.

**Arthritis.** No arthritic changes were seen by roentgen ray. The tissues around the phalangeal joints were swollen tender and painful. There was limitation of motion.

**Atrophy.** Generalized atrophy of skeletal muscles and subcutaneous tissues was present.

**Visual disturbances.** Vision blurred; slight photophobia; spots before eyes occasionally, especially on rising from chair.

**Cyanosis.** There was marked cyanosis of hands and feet without definite border.

**Pain in chest** was absent until three days before death when sudden severe pain occurred in left chest. This was accompanied by dyspnea which persisted until death ensued.

**Vertigo.** There was dizziness on rising from bed or chair; of three months' duration. No loss of consciousness.

Three weeks before death, a complete review of this case by the author led him to the conclusion that the multiplicity of symptoms and signs were largely due to diminished blood flow to the various organs. This was thought to be due to generalized sclerosis of the smaller arteries and arterioles, with resultant narrow-

ing of the lumina. The fever and leukocytosis were considered the result of the urinary tract infection when large numbers of *B. pyocyaneus* were cultured from the urine. The terminal event was bronchopneumonia with pleural effusion.

Dr. Baldouin Lucké, who made the diagnosis on examining the tissues under the microscope, said at the Clinical-Pathological Seminar that the lesions in this patient were more extensive than any he had previously seen.

## SUMMARY

A 63-year-old white woman with fever, leukocytosis, albuminuria, hypertension, edema, loss of weight, neuritis, hematuria, dyspnea, weakness, emaciation, cough, sensory involvement, atrophy, visual disturbances, pain in the chest, vertigo, occult blood in the stools, low normal vasodilatation test and scleroderma was observed over a period of eight weeks. In the fourth week after the onset of objective signs of renal involvement the patient died. Extensive lesions of periarteritis nodosa were found upon microscopic examination of the tissues.

The majority of the signs and symptoms shown by this patient fit into the clinical picture of periarteritis nodosa described in other papers. As Fitz, Parks and Branch<sup>3</sup> quote the original paper of Kussmaul and Maier,<sup>1</sup> "the prognosis is obvious long before its diagnosis can be established."

## BIBLIOGRAPHY

1. Kussmaul and Maier: Ueber eine bisher nicht beschriebene eigenthümliche Arterienerkrankung (periarteritis nodosa), die mit Morbus Brightii und rapid fortschreitender allgemeiner Muskellähmung einhergeht, *Deutsches Arch. f. klin. Med.*, 1:484 (Feb.) 1866.
2. Harris, A. W., G. W. Lynch, and J. P. O'Hare: Periarteritis nodosa, *Arch. Int. Med.*, 63:1163 (June) 1939.
3. Fitz, Reginald, H. Parks, and C. F. Branch: Periarteritis nodosa—report of a case, *Arch. Int. Med.*, 64:1133 (Dec.) 1939.

## Thomas Sydenham to Dr. Cole

. . . I have weighed in a nice and scrupulous balance, whether it be better to serve men, or to be praised by them, and I prefer the former. It does more to tranquillize the mind; whereas fame, and the breath of popular applause, is but a bubble, a feather, and a dream. Such wealth as such fame gives, those who have scraped it together, and those who value it highly, are fully free to enjoy, only let them remember, that the mechanical arts (and sometimes the meanest of them) bring greater gains, and make richer heirs. . . .

January 20, 1681

# Clinicopathologic Conference\*

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## CASE RECORD

A 60-year-old Polish-born janitor entered the Research and Educational Hospital because of: a skin eruption, two years; hair falling out, four months; and "rheumatism" and coldness of feet, five months. Two years prior to admission the skin over the back began to thicken and itch. The lesion spread to involve most surface areas except the palms of the hands and soles of the feet. Four months before admission the scalp became involved and the hair was shed in patchy areas. During this latter period the older lesions became nodular and began to weep. Joint pains in the ankles and feet, associated with a sensation of coldness of the feet, were noted over the five-month period before entrance to the hospital. The patient also complained of "asthma" of six years' duration.

Tonsillectomy was performed six years prior to admission and one year later a "tumor" was removed from the right side of the neck.

Physical examination revealed a well-developed man with generalized skin lesions and marked muscular atrophy. The dermal lesions ranged from pinhead-sized red-brown macules to large firm, marble-sized nodules. Many of the larger lesions were confluent and ulcerated. Such lesions were present on the scalp and there was a patchy type of alopecia. The thorax appeared larger on the right side. Scattered wheezes were heard in both lung fields. The heart was not remarkable, pulse rate 80. The blood pressure was 120/65. The liver was palpated three finger-widths below the costal margin. Pitting edema was present over the feet and ankles. The lymph nodes of the cervical, axillary and inguinal regions were enlarged and firm.

Laboratory Findings. Urine: Sp. Gr. 1.018, Alb.

1+. Examination of the blood revealed a hemoglobin of 11 Gm. and a red count of 3,550,000, white count of 12,500, stab forms 12, neutrophils 52, eosinophils 22, basophils 1, lymphocytes 10, monocytes 3; platelets increased, hematocrit (R) 35 per cent, (W) 2 per cent. Sedimentation rate 30 (corrected). Icterus index—5 units. Sternal marrow: Fat (yellow) 1 per cent, (red) 9 per cent, plasma 27 per cent, "myeloid-erythroid" 30 per cent, erythrocytes 33 per cent. There was some myeloid immaturity with increased numbers of eosinophils. Serum albumin 2.9, globulin 2.8; Kahn test—negative.

An x-ray film showed a tortuous aorta and some left ventricular enlargement. No mediastinal or pulmonary changes were noted. Biopsy of an axillary lymph node was performed. X-ray treatments were given to various portions of the body, and the patient was discharged after a three-month stay in the hospital.

Eight months later the patient was readmitted to the hospital because of progression of his lesions and increasing trouble with his feet. A marked loss of weight and strength had occurred. There was almost complete baldness. The right eyelid was ulcerated and the lips were cracked and dry. Numerous fungating lesions were present over the face, neck, trunk and extremities.

Laboratory Findings. Urine: negative. Blood: Hb. 13 Gm., red count 4,500,000, white count 15,600, with neutrophilic metamyelocytes 4, stab forms 15, neutrophils 22, eosinophils 42 (all mature), basophils 1, lymphocytes 12, monocytes 3. Platelets—adequate. The sternal marrow was hypercellular with numerous eosinophils in all stages of development. No leukemic cells were seen.

The patient failed gradually and expired four weeks after his second admission, nearly three years following the known onset of his disease.

\* Presented November 5, 1946.

## DISCUSSION

DR. SENEAR: The history of a cutaneous disorder beginning with an extensive involvement which is described here as a general thickening of the skin, followed by the development of lesions which are infiltrated plaques or tumors and which eventually break down and ulcerate, would from a clinical standpoint, point to the probability that we were dealing with a case of mycosis fungoides. This disorder is included in the group of what are generally spoken of as the lymphoblastomata, a term originally introduced by Mallory and which later was used by Keim in the dermatologic literature. This term has gained rather wide acceptance, although there are still some who object to the grouping of these several disorders under the single head since this more or less implies that they all have the same genesis or some very intimate relationship. There is still some disagreement as to the relationship between the various members of this group. Others have separated these diseases on a somewhat more restricted basis into the leukemic group, which includes the several types of leukemia, any of which may have associated skin lesions; and then the other group, the lymphomas, includes those disorders in which there are no circulating metastases, so to speak, unlike the leukemic group where, whatever the type, we usually have the changes present in the blood. The lymphomas include the reticulum cell sarcoma or lymphosarcoma and Hodgkin's disease, and some authors include mycosis fungoides in this same group.

As I said, in this case there is a history of onset with itching, accompanied by a more or less generalized eruption (the patient did not speak English very well and it was very difficult to obtain a history of the early involvement) and then there ensued the development of plaques and tumors which eventually ulcerated. This is usually the type of history which we get in mycosis fungoides although itching is frequently the first symptom in any of these diseases. Patients who suffer from any of the members of the lymphoblastoma group not infrequently develop manifestations which are not characteristic of the disease in the sense that they do not have the cellular elements which characterize the disease. These changes have been spoken of as leukemids when they occur in association with leukemia and as pseudoleukemids when they occur in association with Hodgkin's disease. Generally speaking, the term "id" is used here to designate disorders which are toxic in nature due to underlying blood dyscrasias or lymph-node disturbance and which do not contain the basic cellular ele-

ment of the disease. In more recent years it has been recognized that these patients do in some instances have in these nonspecific types of skin involvement the characteristic cellular element of the basic disease. In other words, eruptions clinically so-called "ids" may show true lymphoblastomatous involvement of the skin in exceptional instances. A wide variety of toxic or "id" types of reaction may occur in the lymphoblastomas, for example, petechial hemorrhages, pigmentation, stomatitis. One of the most common and most important symptoms which is present particularly in cases of Hodgkin's disease is the complaint of itching without any eruption. Other "ids" may be maculopapular, vesicular or bullous eruptions, or herpes simplex, herpes zoster, urticaria, and extensive pictures of exfoliative dermatitis, especially the pityriasis rubra or Hebra type of erythroderma.

One of the striking characteristics of this group is that it is impossible from the cutaneous standpoint in many instances to be sure clinically as to whether we are dealing with a leukemia cutis, Hodgkin's disease, lymphosarcoma or with mycosis fungoides. With the last named, we are more apt to make a correct clinical diagnosis since that disorder is characterized by a sequence of several definite stages, the eczematous or premycotic stage, this in turn followed by the stage of infiltration with formation of plaques and the third stage in which the tumors develop. On the other hand, we have patients who present clinically mycosis fungoides as in the case here, whereas histopathologically the findings may point to some other member of the group.

Another common characteristic of these disorders is the extreme radiosensitivity of the lesions since so small a dose as 75 roentgens will often cause a very rapid disappearance of lesions. Often a large tumor will completely disappear with 75 to 150 roentgens, which would not occur in most other conditions, particularly tumors of other types. Another thing which we have to bear in mind in these cases is that they may change in their clinical aspect from time to time so that as we see these patients we occasionally make a diagnosis of mycosis fungoides and later on may wish to change the diagnosis, from a clinical standpoint, to Hodgkin's disease, lymphosarcoma or leukemia.

It would seem as though the blood picture would clinch the diagnosis in cases in which we feel that the skin lesions definitely belong in the group of the leukemias. However, it must be recalled that Arndt at an earlier date pointed out that there are aleukemic, subleukemic and leukemic types of blood pictures in

patients showing leukemia cutis. In the aleukemic variety there is no increase in the number of white cells and the proportions of the various types of cells are within normal limits. In the subleukemic variety there is no actual increase in the number of white cells but the lymphatic cells show a proportional increase. In the leukemic variety there is, of course, an actual increase in the number of white cells due to the presence of an increased number of lymphatic cells.

In order to reach a definite diagnosis in many of these cases, it is necessary to have the opportunity for prolonged observation and close co-operation with pathologists before a definite diagnosis can be reached. I recall a patient whom I had in the hospital several years ago who had a generalized exfoliative dermatitis accompanied by lymphadenopathy. The biopsy of material from the skin showed a nonspecific picture of chronic dermatitis. Consequently, one of the enlarged nodes in the inguinal region was removed and the first report from the pathology laboratory stated unequivocally that the picture was that of lymphosarcoma. At that time a distinguished pathologist from another city happened to be visiting here and he, together with one of our senior pathologists, felt that the microscopic picture indicated definitely that the condition was some member of the lymphoblastoma group but they felt that they could not give it any specific designation at that time. It is a common experience to have disagreement among pathologists when tissue, either from the skin or from the nodes in cases of lymphoblastoma are examined.

Going back to the clinical aspects, we find that ulceration tends to occur more readily in some types than others. Ulceration is seen most frequently in the lesions of mycosis fungoides and not infrequently in the cutaneous lesions of Hodgkin's disease. Ulceration in lesions of leukemia cutis are seen somewhat less frequently than is the case in Hodgkin's disease and much less frequently than in mycosis fungoides. In most instances the cutaneous lesions in these diseases are very numerous but in some instances only a single lesion may occur.

Insofar as the differential diagnosis is concerned, with the description of the lesions and the history as given in the protocol, there are very few things which might be thought of as alternative diagnoses. Leprosy may be suggested by some cases of leukemia cutis where lesions of the latter disorder, occurring in the supra-orbital region, may give the characteristic leonine facies seen in leprosy. The histopathologic findings, together with the presence, in mixed types of leprosy at least, of such changes as atrophy of the

interosseous muscles or enlargement of the ulnar or great auricular nerves may serve to differentiate the two. One should always keep in mind in the differential diagnosis the possibility of a late type of cutaneous syphilis. A history of itching preceding development of the lesions here would speak very much against the diagnosis of syphilis. Likewise, the bilateral and symmetrical distribution of the lesions are not apt to be found in late syphilis. Likewise, the ragged and undermined character of the margins of the ulcers rather than the sharply punched out type seen in syphilis, would not fit in with the diagnosis of syphilis.

I feel that from the clinical standpoint, this case can be definitely diagnosed as one of lymphoblastoma, and that it could safely be designated as typical of mycosis fungoides from the clinical standpoint.

DR. BENNETT: From the abstract of this patient's record it is apparent that rather careful hematologic studies were made. I wonder if Dr. Limarzi would care to comment on the recorded blood and sternal marrow findings.

DR. L. R. LIMARZI: From a hematologic point of view there is very little in the blood or bone marrow that is of diagnostic importance in this case, but since the impression is that this is a case of lymphoma, perhaps we had better say a few words about the blood and bone marrow findings in this group of diseases.

It is interesting that very often the doctors in the dispensary send us cases in which the diagnosis is one of the lymphoblastoma group, with a note to either confirm or rule out the diagnosis. I emphasize this because there is nothing in the blood or bone marrow that is diagnostic of Hodgkin's disease, lymphosarcoma or mycosis fungoides. The only member of this group that presents anything characteristic in the blood and bone marrow is lymphatic leukemia. Very often in cases of Hodgkin's disease, the peripheral blood may show at some time during the course of the disease, a monocytosis, eosinophilia, or a polymorphonuclear leukocytosis. The latter is seen during the terminal phase of the disease. Occasionally one sees abnormal forms of platelets in the blood. The bone marrow is hyperplastic and may show an increased number of eosinophils, histiocytes or reticulum cells, and plasma cells. Very often the megakaryocytes are increased with a myeloid immaturity in the bone marrow. These findings are in no way diagnostic of Hodgkin's disease.

In the case of lymphosarcoma the blood and bone marrow is not diagnostic, except when the condition is converted into lymphosarcoma cell leukemia or leukosarcoma; then the blood and bone marrow is

that of a leukemia. This may occur spontaneously or following x-ray treatment. In the case of mycosis fungoides neither the blood nor the bone marrow is of diagnostic importance. In other words, we may say that with the exception of lymphatic leukemia, the diagnosis can only be made from a histologic section. We can use the words of the roentgenologist and say that certain findings in the blood and bone marrow are consistent with/or suggestive of one of the lymphomas when the clinical findings fit into one of the groups, but I must emphasize that in the last analysis the final diagnosis will rest on the histologic section.

DR. BENNETT: Dr. Harvey, will you show the x-ray films?

DR. R. HARVEY: There are two chest x-ray pictures taken on this patient eight months apart. Although slight enlargement of the left ventricle and slight tortuosity of the aorta are mentioned in the protocol, neither of those changes are unusual in degree for a patient of 60 years of age. Throughout both lung fields there are increased bronchial vascular markings which extend to the periphery of both lung fields and there is obliteration of the left costophrenic sinus, probably the result of pleurisy. These changes, plus increased radiolucency in the lung fields, are consistent with mild emphysema, and acute and chronic bronchitis. I doubt that these films show anything remarkable as far as the main disease is concerned because of:

1. The lack of any great change in these two films in the eight months' interval.
2. Absence of any lymph-node enlargement in the mediastinal area.
3. Lack of hilar enlargement or radial type of infiltrating shadows from those zones.

### ANATOMIC FINDINGS

DR. BENNETT: The pathologic features of the underlying disease process in this case can be demonstrated only in the microscopic sections and with the aid of photomicrographs. These will be shown later. First I would like to comment on the gross changes and the lesions that were responsible for the death of the patient.

Examination of the body revealed some increase of pigmentation of the skin and loss of hair. Scattered over the entire body were lesions varying in diameter from 1 mm. or less to 2 or 3 cm. Many of the larger lesions had firm elevated margins surrounding depressed ulcerated centers. Such lesions were more numerous on the extremities but they were present also on the scalp and trunk. All of the lesions were superficial and could be moved freely with the skin.

The dermal tissues between the nodules seemed somewhat thickened and inelastic. These photographs show the lesions that were present on the forearms (Fig. 1). Dr. Sencar, would you care to comment on these photographic reproductions?



FIG. 1. Gross photograph reproduced from a kodachrome reproduction showing the tumorous nodules in the skin of the forearm, neck and face. One should also note the evidences of dermatitis in the remaining parts of the skin surface.

DR. SENCAR: The only comment that I might make here is that the pictures clinically suggest mycosis fungoides rather than Hodgkin's disease, but as previously indicated, it is not always possible to make a clean-cut differentiation. In mycosis fungoides, however, we have a particular tendency to the development of arciform and annular configuration in the lesions, and the presence of such types here is very suggestive. Furthermore, in mycosis fungoides, we see occasionally, in the late stages, a tendency for the development of fungating lesions. Mycosis fungoides would unquestionably be suggested as the most probable diagnosis with Hodgkin's disease of the skin as the second possibility.

DR. BENNETT: Gross examination of the internal organs revealed little of significance. The heart weighed 280 Gm. and appeared normal in shape. However, on section there was a small area of fibrosis along the left border of the left ventricle. This was undoubtedly the result of an old infarct.

Dr. Harvey has called attention to increased bronchovascular markings in the lung fields in the x-ray films. Our examination of the lungs revealed, in addition to a diffuse purulent bronchitis and bronchopneumonia, an increase in the prominence of the bronchi. Microscopic examination indicated that

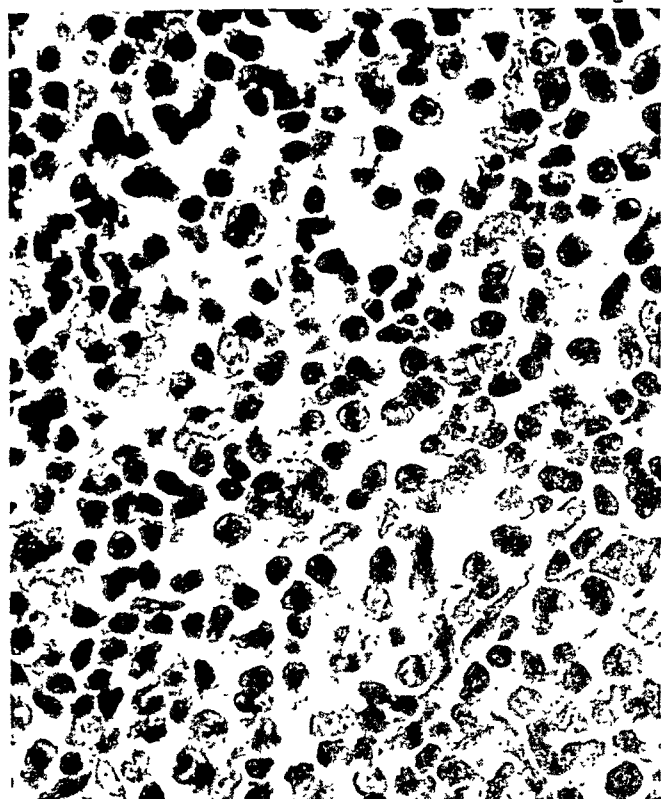


FIG. 2. Photomicrograph of an axillary lymph node removed for biopsy. The variable cytologic picture is made up of eosinophils, lymphoblasts, mature lymphocytes, and plasma cells. Mitotic figures also are in evidence.

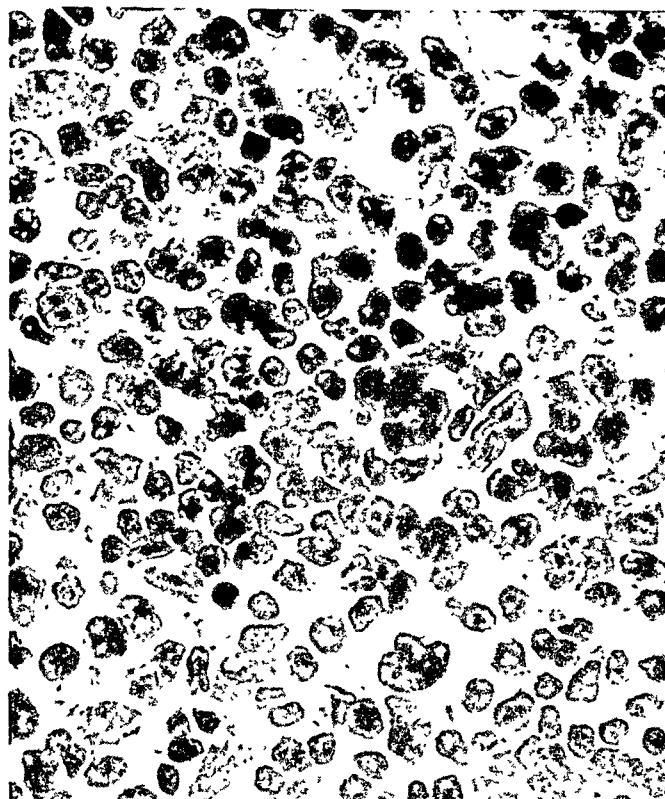


FIG. 3. Photomicrograph of an inguinal lymph node removed at autopsy. A somewhat more uniform replacement of the lymphoid tissue by abnormal cells is present. One cell with an irregular nucleus resembling a Reed-Sternberg cell is evident in the lower portion of the photograph.

this prominence was caused by an extensive peribronchial infiltration with lymphocytes. Many of the infiltrating cells were immature and resembled those observed in the tumorous nodules in the skin and in the lymph nodes. Eosinophils and plasma cells were present in excessive numbers among the lymphoid cells. In addition to these changes some of the bronchi contained exudate that was undergoing organization. These changes undoubtedly explain the findings in the x-ray films and they may also explain the patient's symptoms of asthma. The right pleural cavity contained 2,000 cc. of turbid fluid containing flakes and strands of fibrin. Cultures of this fluid and of the heart's blood yielded beta hemolytic streptococci.

The liver was normal in size. It was not remarkable on gross inspection. On microscopic examination there were small scattered accumulations of lymphocytes, lymphoblasts, plasma cells and eosinophils in a few areas. These cellular accumulations were more frequent in the periportal zones.

The spleen weighed 200 Gm. No significant lesions were noted on either gross or microscopic examination.

No pathologic changes other than scarring from arteriosclerosis were present in the kidneys.

The inguinal and axillary lymph nodes were considerably enlarged. Each of these areas contained 12 or more hypertrophied nodes that ranged up to  $3 \times 2$  cm. in greatest dimensions. On gross section these nodes were pale and homogeneous. Microscopically, they were largely replaced by closely packed cells obscuring the normal architecture. The microscopic changes, while not characteristic of Hodgkin's disease, resembled that condition more closely than any other form of lymphoma. Lymphoblasts, plasma cells and eosinophils were exceedingly numerous. Occasional large cells with lobated nuclei resembling Reed-Sternberg cells were seen. Mitotic figures were numerous (Fig. 2, 3). It is worthy of note that lymph node enlargement was minimal in the mesenteric, mediastinal and peribronchial areas and in these regions there was no evidence of tumor replacement of the nodes.

Microscopic sections of the dermal tissues showed lesions varying from a scant infiltration of the corium with lymphocytes, plasma cells and eosinophils to



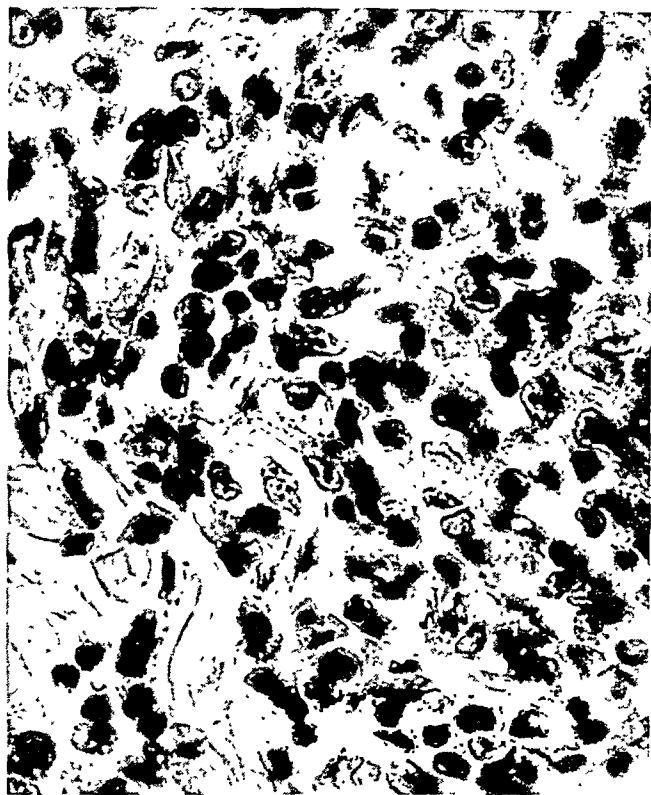


FIG. 4. Tumor cell infiltration of the collagen of the corium is evident in this photomicrograph.

bulky tumorous lesions comprised largely of lymphoblasts and more mature lymphocytes. In the larger lesions the corium was invaded deeply and the epidermis was pushed upward (Fig. 4). A tendency for extension of the infiltrating cells along sweat gland ducts and blood vessels was clearly evident.

Sections of bone marrow revealed an occasional focal accumulation of cells of the type forming the lymph node and dermal lesion.

We have concluded from these findings that the basic lesion is a lymphoblastoma affecting primarily the dermal structures and superficial lymph nodes. Although not entirely compatible with Hodgkin's disease, the cytologic picture resembled Hodgkin's disease more closely than any other process. Because of the long-standing dermatitis and the disproportionate involvement of the skin, we have further classified this case as an example of mycosis fungoides.

The patient passed through the three stages referred to by Dr. Senear and reached the stage of cachexia, frequently regarded as the fourth stage of mycosis fungoides. The terminal event was infection producing pneumonia, fibrinopurulent pleuritis and bacteremia.

DR. R. W. KEETON: It is of interest that all the pathologic findings in this man's case were in the skin and subcutaneous tissues. The remainder of the

body was relatively normal except for terminal changes. This demonstrates that changes in the skin may lead to death. One can see the pathologic alterations which indicate that autolytic changes are occurring. These, in turn, liberate products which lead to gradual wasting and death. It is not entirely clear as to how much weight should be attached to the absorption of toxic products and how much to alteration in the function of the skin.

The skin and subcutaneous tissues are storehouses for extra blood. Through them heat is eliminated, water is lost, and other functions are performed. One can easily see that with a derangement in these functions considerable stress may be thrown on other organs of the body.

A patient was recently seen with an exfoliative dermatitis of the type of pityriasis rubra. It was thought that his skin condition was to be attributed to a lymphoblastoma. However, it was associated with a vitamin D intoxication. With the correction of the vitamin D intoxication the skin condition began to clear. The regression in the symptoms appeared to be primarily correlated with the improvement in the skin condition. The recovery in the kidney function required a much longer time and was still not complete after a general symptomatic recovery had occurred.

DR. SENEAR: (Closing remarks). As Dr. Bennett has pointed out, mycosis fungoides is recognized now as a disease which may involve any part of the body. It was originally looked upon as a disorder limited to the skin and as recently as eight to ten years ago dermatologic literature referred to mycosis fungoides as a purely cutaneous disorder. Recent publications, however, have recognized that the skin picture is often only part of a more extensive involvement. Furthermore, some authors have felt that mycosis fungoides is actually a form of Hodgkin's disease and this conception, of course, would indicate that mycosis fungoides is capable of involving organs other than the skin.

#### DR. SENEAR'S DIAGNOSIS

##### 1. Lymphoblastoma—Mycosis fungoides.

#### ANATOMIC DIAGNOSES

1. Cutaneous lymphoblastoma (mycosis fungoides) involving axillary and inguinal lymph nodes and bone marrow.
2. Chronic and acute purulent bronchitis.
3. Bronchopneumonia.
4. Acute fibrinopurulent pleuritis.
5. Bacteremia (beta streptococcus).
6. Healed myocardial infarct (left ventricle).

# Prematurity from the Viewpoint of the Obstetrician\*

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It is common knowledge that prematurity is the principal cause of death in the neonatal period, accounting for about one-half of all fatalities occurring at that time. During the past decade pediatricians and public health officials have made significant inroads on this toll, but they would be the first to affirm that the salvage, particularly in the smaller weight groups, is still discouragingly small. There are two main ways of attacking this problem. In the first place, mortality rates could be lowered substantially by wider dissemination of existing knowledge together with better distribution of personnel and facilities. This is a pediatric and public health responsibility. The other means by which premature mortality might conceivably be reduced is through the prevention of premature birth—obviously a challenge to the obstetrician.

It is the purpose of this paper to review the experience of the Johns Hopkins Hospital with premature birth during the past 20 years for the purpose of ascertaining, if possible, those factors which are most frequently responsible for this accident. Only when these factors are clearly understood, of course, can any intelligent attempt at prevention be made. In addition, opportunity will be taken to discuss how premature labor may best be managed to the end that the infant will have the greatest likelihood of survival.

## KNOWN CAUSES OF PREMATURITY

Between June 1, 1926 and December 31, 1945, among 28,493 total deliveries, 3,331 premature infants (1,000–2,499 Gm.) were born—giving a gross incidence of 11.7 per cent (Table 1). This figure, however, is rather meaningless because of the heterogeneous nature of the cases. In some of these premature births, for instance, labor started spontaneously, whereas in others it was initiated artificially or cesarean section performed because of maternal disease. A certain proportion of the cases were twin pregnancies. Moreover, there were wide racial, social and economic differences among the patients, all of

which might conceivably have a bearing on the etiology of prematurity. Hence, if we are interested in looking into the causation of prematurity, it becomes necessary to break the series down into smaller groups.

TABLE 1

### *General Incidence of Prematurity*

Total infants born.....	28,493
Premature infants (1,000–2,499 Gm.).....	3,331 (11.7%)

TABLE 2

### *Prematures Divided into Three Major Etiologic Groups*

	INFANTS	% OF TOTAL PREMATURES
Spontaneous termination of pregnancy, 2,457 single pregnancy only		73.8
Operative termination of pregnancy, 478 single pregnancy only		14.3
Multiple pregnancy, both spontaneous and operative termination	396	11.9

As may be seen in Table 2, the 3,331 infants fall into three main categories if considered from the viewpoint of known etiology. Reading this table from below upwards, it will be seen that 11.9 per cent of the cases were multiple gestations; in about 90 per cent of these the onset of labor was spontaneous, in the remainder operative. It is well known, of course, that twin pregnancies terminate, on the average, about 3 weeks before the expected date of confinement because of over-distention of the uterus. From the viewpoint of prognosis, such infants are almost always of greater gestational age than their individual weights would indicate and hence have a better chance of survival. For this reason, and also because nothing can be done to prevent over-distention of the uterus under such circumstances, this rather special group of premature infants needs no further discussion.

Table 2 shows also that in approximately one-seventh of the cases, premature delivery was effected artificially because of maternal disease. The more common complications which seemed to necessitate this step are shown in Table 3. In over one-half of the premature operative deliveries intervention was

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carried out because of toxemia of pregnancy, while in 18.4 per cent it was done because of placenta previa and premature separation of the placenta. These three conditions then (toxemia, placenta previa, abruption placenta) account for over two-thirds of the

TABLE 3

*Common Conditions Necessitating Premature Operative Termination of Pregnancy. Single Pregnancy Only*

Total Cases of Premature, Operative Termination of Pregnancy			478
DISEASE	CASES	PER CENT	
Pre-eclampsia and eclampsia	152	31.8	
Chronic hypertension	100	20.9	
Placenta previa	60	12.5	
Premature separation	28	5.9	
Total due to diseases listed	340	71.1	

cases in which premature delivery was effected artificially. Today, with the ready availability of blood banks, it is possible that some of the cases of placenta previa might have been carried to maturity without great risk to the mother; but even if all had been brought successfully to term, the number of premature births so prevented (60) is almost negligible when compared with the total of 3,331 premature infants in the series. In so far as toxemias are concerned, it is our carefully considered opinion that any extended attempt to carry many of these patients to term would have resulted in grave risks to the mother. In sum, for this group of premature births which are chargeable to obstetrical intervention, it seems unlikely that any substantial reduction in this group can be expected (with the possible exception of a few cases of placenta previa) until the etiology and prevention of the toxemias and abruption become known.

Turning now to the first item in Table 2, it will be seen that 73.8 per cent of the 3,331 premature in-

fants or approximately three-quarters, were cases in which the labors were of spontaneous onset and the pregnancies single. What caused labor to start prematurely in these 2,457 gravidæ? As shown in Table 4, this question can be answered specifically, in only 343 cases or 14.0 per cent. In evaluating this table it is important to recall that the simple association of premature labor and some complication of pregnancy does not necessarily mean that that complication was the cause of the premature parturition. Such a causal relationship can be postulated only if it can be shown that a given complication precedes premature labor much more frequently than would ordinarily be expected. On the basis of figures which will be presented shortly (Table 6), it can be calculated that the incidence in our general clinic population of spontaneous premature labor with single pregnancies, is 10 per cent—7.2 per cent in white patients and 13.4 per cent in negroes. This figure of 10 per cent was taken as the frequency with which premature labor would ordinarily be expected with the exception of the group with syphilis; here, because of the great racial difference the race-specific figures have been used. As an example of the method used to calculate the number of premature labors which could be attributed to these several diseases, let us take the 89 cases with placenta previa. We would expect, on the basis of the general clinic figure, that 10 per cent or 9 would have premature infants. Actually, 45 had, or 36 more than would be expected. Applying the same method of approach to the other conditions listed, we arrive at the total number of spontaneous labors, with single pregnancies, in which one or another disease process can definitely be incriminated as the cause of the premature labor, namely, 343.

The findings in pre-eclampsia—one of the two most common complications listed in Table 4—indicate that this condition is rarely *per se* the cause of pre-

TABLE 4

*Role of Various Diseases in Causing Prematurity. Spontaneous Termination of Pregnancy, Single Pregnancies Only. (Expected incidence on basis of general clinic population would be 10.0 per cent; in white 7.2 per cent, in negroes 13.4 per cent)*

DISEASE	TOTAL CASES (1)	PREMATURES EXPECTED (2)	PREMATURES FOUND (3)	PER CENT FOUND (4)	PREMATURES DUE DISEASE (3-2)
Placenta previa	89	9	45	50.6	36
Premature separation	109	11	67	61.5	56
Pre-eclampsia	2,195	220	264	12.0	44 (?)
Eclampsia	107	11	27	25.2	16
Chronic hypertension	545	55	115	21.1	65
Syphilis—Negro	2,142	287	368	17.2	81
Syphilis—White	268	19	34	12.7	15
Heart disease	407	41	71	17.4	30
Total prematures due to disease					343
Per cent of prematures (2,457) with spontaneous onset of labor, single pregnancies only					14.0

mature labor since the 12 per cent of prematures found in this group is not significantly higher than the 10 per cent expected. It is true, as shown in Table 3, that pre-eclampsia is responsible for a substantial number of premature births through necessitating therapeutic termination of pregnancy; but this in no way nullifies the statement that this disease shows no appreciable tendency *per se* to initiate premature labor. In a recent study by Brown, Lyon and Anderson<sup>1</sup> on the influence of toxemia on the incidence of prematurity, the frequency of prematurity was found to be essentially the same among the offspring of women with mild toxemia as among those who did not have toxemia. The severer grades of toxemia in their series, however, were associated with definitely higher rates of prematurity. But these authors included in these calculations not only cases in which labor started spontaneously but also those in which therapeutic induction of labor was carried out. The latter procedure was effected in 31, or 11 per cent of their total number of 280 patients with toxemia. Since therapeutic interruption of pregnancy is more frequently necessary in the severer forms of pre-eclampsia, it seems probable that re-calculation of their results after deletion of these 31 cases would yield figures very comparable to ours as far as pre-eclampsia is concerned. In eclampsia and chronic hypertensive vascular disease the incidence of spontaneous premature labor appears to be about twice the usual frequency. It should be noted that the proportion of patients with syphilis who gave birth to premature infants is relatively small—17.2 per cent in negroes and 12.7 per cent in white women. These figures are only slightly higher than the percentages which would ordinarily be expected, 13.4 and 7.2 per cent, respectively. It is obvious that we are dealing with treated syphilis for the most part in these two-thousand-odd luetics.

Let us now add up all the known causative factors of premature birth in this total series as discussed in the foregoing paragraphs. This summary is shown in Table 5. (Fifty-two cases of congenital abnormalities incompatible with life are listed in addition to the groups already discussed.) It is here apparent that in our series of 3,331 premature infants, a definite cause of the premature delivery was demonstrable in only 1,269, or 38.1 per cent.

When one attempts to compare this figure of 38.1 per cent with corresponding figures which have been reported, almost incredible disparities are encountered. In a review of the literature on the causes of prematurity, Anderson and Lyon<sup>2</sup> summarized the data from 27 papers and found that the frequency

TABLE 5  
*Summary of Known Causative Factors*

Total premature infants, 3,331		
CAUSE OF PREMATURE BIRTH	INFANTS	PER CENT
Maternal disease; spontaneous onset (Table 4)	343	10.3
Maternal disease; operative termination (Table 3)	478	14.3
Congenital abnormality	52*	1.6
Multiple pregnancy (Table 2)	396	11.9
Total	1,269	38.1

\* Estimated on basis of 26 for second ten-year period; comparable figures for first ten-year period not available.

with which investigators could assign definite causes for their premature deliveries ranged between 7.2 and 80.2 per cent (!) with all gradations between. One cause for this extreme variation, particularly the higher figures, is that many authors have overlooked the fact, already stressed, that the mere association of premature labor and some disease does not necessarily incriminate that disease as the causative agent. For instance, in many reports, all premature deliveries associated with toxemia are attributed to that complication and all premature births in which the mother had a positive serologic test for lues, with or without treatment, are attributed to syphilis. Had the same principle been followed in this study, we would have been able to explain all the premature deliveries listed in Column 3, Table 4, or 991, instead of 343. If this number of 991 be substituted for the latter figure in Table 5, we could account for 1,917, or 57.6 per cent of our 3,331 cases. But, as we have seen, this approach is without justification; and, in our opinion, the figure here presented—namely, about 40 per cent of premature births explained—is a valid and fairly accurate approximation of the state of affairs as they exist in the country at large.

If this be true, in about 60 per cent of all premature births no specific explanation for the accident can be educed. What can be the cause of the early onset of labor in these cases? In all medicine there is surely no more important problem than this since it entails a threat to the lives of some 150,000 babies annually in this country alone.

#### ECONOMIC AND RACIAL FACTORS AS CAUSES OF PREMATURITY

In an effort to inquire into the possible roles played by economic and racial factors, in premature births, our 2,457 cases in which the pregnancy was single and the onset of labor spontaneous have been divided into three main groups—private patients, white ward pa-

TABLE 6

*Incidence of Prematurity according to Economic Status and Race*  
(Spontaneous onset of labor, single pregnancies only)

BABY WEIGHT	PRIVATE		WHITE WARD		NEGRO WARD	
	CASES	%	CASES	%	CASES	%
2,500+ Gm.	2,040	94.7	9,898	92.4	9,926	86.6
1,000-2,499 Gm.	114	5.3	810	7.6	1,533	13.4
Total	2,154	100.0	10,708	99.9	11,459	100.0

tients and colored ward patients, and the incidence of prematurity in the three classes studied. As shown in Table 6, the frequency of premature delivery rises rather steeply as one goes from private to white ward to colored ward patients; indeed, the incidence is 50 per cent higher in white ward than in private patients, and in negroes two and a half times as high.

A number of objections will be raised against these figures. The most obvious is that the same criterion of prematurity has been used for white as for colored babies, that is, the birth weight under 2,500 Gm., whereas it has been shown on the basis of ossification centers and on other grounds that this figure for negro infants should be nearer 2,350 Gm. We can hence be criticized for including in our negro premature group, a goodly number of infants weighing between 2,350 and 2,499 Gm. who by many authorities would not be regarded as premature at all. While this criticism is a valid one, we do not believe it accounts for the tremendous differences shown in Table 6. Moreover, the same differential, as shown in Table 7, is demonstrable in all weight groups. Certainly, the degree of prematurity represented by these several weight groups must be approximately

TABLE 7

*Incidence of Various Degrees of Prematurity according to Economic Status and Race.* (Spontaneous onset of labor, single pregnancies only)

BABY WEIGHT	PRIVATE		WHITE WARD		NEGRO WARD	
	CASES	%	CASES	%	CASES	%
2,500+ Gm.	2,040	94.7	9,898	92.4	9,926	86.6
2,000-2,499 Gm.	82	3.8	525	4.9	1,024	8.9
1,500-1,999 Gm.	22	1.0	195	1.8	351	3.1
1,000-1,499 Gm.	10	0.5	90	0.8	158	1.4
Total	2,154	100.0	10,708	99.9	11,459	100.0

the same because the mortality rates, as shown in Table 18, are very similar; however, the somewhat lower mortality rate of negro infants in the 2,000-2,499 Gm. group, may well indicate the inclusion here of a small number of actually mature babies. Another criticism which may be made of Tables 6 and 7 is that several other studies have failed to reveal a racial difference in the incidence of prematurity. It

is important to make it plain at this point that we do not regard the difference under discussion so much racial as economic. The income levels of our colored ward patients is definitely below that of our white ward clientele and by the same token their housing conditions, diet, ways of living, etc. If I am not mistaken, the same striking difference in economic status does not apply to many of the race groups which have been studied elsewhere.

Still another objection which may be leveled at Tables 6 and 7 is that there are included here a large number of premature births which were the spontaneous result of maternal disease and that the differences shown may actually be due to an unequal incidence of these diseases in the three groups rather than to any intrinsic factor due solely to inequalities of economic status. A case in point would be syphilis which could conceivably account for a good part of the difference between the incidence of prematurity in private patients, who rarely have positive serology, and in our negro ward patients, who show positive tests for syphilis in over 20 per cent of cases. In order to eliminate this source of error, Table 7 has been redone eliminating all cases in which any of the complications listed in Table 4 was present. The results are shown in Table 8. It will be seen that the same differential between the three economic groups is still demonstrable; and the inference would seem inescapable that there is some factor, or factors, associated with economic level—quite apart from all the known causes of prematurity—which has an important bearing on the frequency of this accident.

TABLE 8

*Incidence of Prematurity according to Economic Status and Race in Cases without Demonstrable Cause for Premature Birth.* Spontaneous onset of labor, single pregnancies only, with all cases complicated by diseases listed in Table 4 eliminated. (June 1, 1936-December 31, 1945).

BABY WEIGHT	PRIVATE		WHITE WARD		NEGRO WARD	
	CASES	%	CASES	%	CASES	%
2,500+ Gm.	1,903	95.5	4,130	93.2	3,484	88.2
2,000-2,499 Gm.	65	3.3	201	4.5	327	8.3
1,500-1,999 Gm.	17	0.9	68	1.5	92	2.3
1,000-1,499 Gm.	7	0.3	32	0.7	46	1.2
Total	1,992	100.0	4,431	99.9	3,949	100.0

Further, and perhaps more convincing, evidence in regard to the role played by economic and social factors in the causation of premature birth is shown in Table 9. Here the incidence of prematurity in our series is presented according to whether the patients had no prenatal care (no visits), poor prenatal care (1 or 2 visits) or adequate prenatal care (3 or more visits). The findings were dramatic beyond all ex-

TABLE 9

*Incidence of Prematurity in Relation to Prenatal Care*  
Spontaneous onset of labor, single pregnancies only

BABY WEIGHT	NO CARE (NO VISITS)		POOR CARE (1-2 VISITS)		ADEQUATE CARE (3+ VISITS)	
	CASES	%	CASES	%	CASES	%
2,500+ Gm.	963	73.6	1,396	76.2	17,528	92.2
2,000-2,499 Gm.	154	11.8	239	13.0	1,115	5.8
1,500-1,999 Gm.	110	8.4	129	7.0	287	1.5
1,000-1,499 Gm.	81	6.2	68	3.7	87	0.5
Total	1,308	100.0	1,832	99.9	19,017	100.0

pectation, showing that among our patients who had no or poor prenatal care, the incidence of premature birth was 24.9 per cent (almost exactly one-quarter!), whereas, in women with good care it was only 7.8 per cent. We have tried to explore all possible sources of error which might bear on the validity of these figures but without appreciable success. Certainly, there is no racial factor here since our negro patients make, on the average, more visits than our white patients. Lest it be thought that the patients who had no prenatal care represented mostly emergency admissions for placenta previa, abruptio and eclampsia, conditions known to cause prematurity, Table 10 has been

TABLE 10

*Incidence of Prematurity in Cases without Demonstrable Cause for Premature Birth, in Relation to Prenatal Care.* Spontaneous onset of labor, single pregnancies only, with all cases complicated by diseases listed in Table 4, eliminated. (June 1, 1936-December 31, 1945).

BABY WEIGHT	NO CARE (NO VISITS)		POOR CARE (1-2 VISITS)		ADEQUATE CARE (3+ VISITS)	
	CASES	%	CASES	%	CASES	%
2,500+ Gm.	234	76.5	330	70.7	7,440	93.3
2,000-2,499 Gm.	32	10.5	69	14.8	417	5.2
1,500-1,999 Gm.	20	6.5	46	9.8	89	1.1
1,000-1,499 Gm.	20	6.5	22	4.7	28	0.4
Total	306	100.0	467	100.0	7,974	100.0

prepared. This shows the incidence of prematurity according to the quality of prenatal care in patients who had no demonstrable cause for the accident. Although the number of patients with poor or no prenatal care now becomes rather small for significant statistical analysis, it is still clear that about one-quarter of our patients in this category have premature deliveries in contrast to about 7 per cent in women who have had adequate care. The figures in Tables 9 and 10 may be effected to some degree by the fact that the women who delivered prematurely did not have as many months over which to make prenatal visits as did the patients who went to term, but if they registered reasonably early they had ample

time to get in at least three monthly visits before going into premature labor. In any event, this possible source of error can account for only a small fraction of the differences shown in Table 9 and would be applicable to but a very small minority of our patients who register late.

How then are we to account for these striking differences between the frequency of prematurity between patients with good and poor prenatal care? It may be that the instructions which patients receive at "Mothers' Classes" in regard to diet and hygiene help a great deal, but it seems unlikely that this is the whole answer. A more rational explanation would seem to lie in the general characteristics, as a class, of those patients who habitually neglect to seek medical attention, such as prenatal care, though it is known to be available. They are, in the main, the shiftless and improvident of our populace notorious to every social worker; and their habits of living in general are doubtless just as ill managed as their habits in relation to prenatal care.

It was presumably these irresponsibles then, who gave birth, in our series at least, to premature infants in one pregnancy out of four. But why? It is certainly not excessive work, because with occasional exceptions this group is not so addicted. It occurred to us that it might be too frequent coitus. This is a question impossible to answer definitely but it is interesting to note that more or less complete abstinence from coitus does not reduce the frequency of premature birth. This is brought out in Table 11 in which we have used our series of illegitimately pregnant white patients (mostly Florence Crittenton cases) as examples of women in whom coitus during pregnancy is probably rare. This table indicates that in this limited experience marital status had no significant bearing on the incidence of prematurity.

TABLE 11

*Incidence of Prematurity in Unmarried White Ward Patients*  
June 1, 1936 to December 31, 1945

BABY WEIGHT	CLINIC POPULATION WHITE WARD ONLY		UNMARRIED WHITE WARD	
	CASES	%	CASES	%
2,500+ Gm.	9,898	92.4	544	91.1
2,000-2,499 Gm.	525	4.9	38	6.4
1,500-1,999 Gm.	195	1.8	7	1.2
1,000-1,499 Gm.	90	0.8	8	1.3
Total premature	810	7.6	53	8.9

## DIETARY DEFICIENCY AS A CAUSE OF PREMATURE LABOR

In seeking an explanation for the striking difference in the incidence of prematurity between our patients

with adequate and with little or no prenatal care, we have taken particular note of the fact that the irresponsible group who neglect prenatal care are also, in the main, the lower economic group and that, therefore, Tables 6, 7 and 8 (economic factors) corroborate Tables 9 and 10 (lack of prenatal care as a factor). In other words, our findings indicate from two different approaches that the incidence of prematurity augments as economic levels descend. As shown by McCance and his associates,<sup>3</sup> economic level exerts an important influence on the intake of essential food elements such as minerals, vitamins and proteins and in a study of the diets of a large number of pregnant women at various economic levels, he found that "a rise in spending power led to an increased consumption of milk, fruit, vegetables and meat, and a decreased consumption of bread and total cereals."

Taken alone, the findings in the present paper cannot be accepted as establishing a relationship between dietary deficiencies and premature labor, but when considered in correlation with other types of evidence, the conclusion is inescapable that faulty nutrition deserves serious consideration as a possible cause of the dramatic differences in the incidence of prematurity which we have just discussed. Thus far, indeed, it is the only one we have to suggest.

The other types of evidence indicating that dietary deficiencies may cause premature labor are many and varied. The records of animal experimentation are replete with illustrations of fetal damage resulting from prenatal dietary deficiencies of various types.<sup>4-7</sup> Evidence of damage to the human fetus also, due to inadequate maternal nutrition in pregnancy, has been reported.<sup>8-11</sup> In the last few years several prenatal studies on large numbers of women have been carried out which have included evaluation of their diets during pregnancy. The first reports of this type to gain widespread attention were the Toronto studies of Ebbs, Tisdall and their co-workers.<sup>12-15</sup> A group of 120 women on poor diets and low incomes were studied during the last half of pregnancy as controls for 90 women from the same income level and on equally poor diets who were supplied with supplementary rations of milk, cheese, oranges, tomatoes, wheat germ and vitamin D capsules, and 170 women with fairly adequate incomes who were instructed in the type of diet considered desirable for pregnancy. The findings in relation to the question at hand were most dramatic: the incidence of premature births in the women with poor diets was 8.0 per cent, in those with supplemented diets 2.2 per cent and in those with good diets, 3.0 per cent. The corresponding figures for miscarriages were 6.0, 0.0 and 1.2 per cent and for stillbirths 3.4, 0.0 and 0.6 per cent. In an

often-quoted paper by Burke and her associates,<sup>16</sup> a statistically significant relationship has been shown between the diet of the mother during pregnancy and the condition of the infant at birth and during the first two weeks of life. In the 216 cases considered in that study, let it be noted, all stillborn infants, all infants who died within a few days of birth except one, most infants who had marked congenital defects, *all premature*, and all functionally immature infants were born to mothers whose diets during pregnancy were very inadequate.

A number of mass studies of the outcome of pregnancy in relation to diet have been made, notably in England, with similar findings. The People's League of Health of England<sup>17</sup> investigated the effect of the nutrition of 5,022 pregnant women upon maternal and infant morbidity and mortality. Supplementary minerals and vitamins were given to one-half of the women studied. This supplementary feeding tended to reduce the incidence of toxemia approximately 30 per cent while the reduction in the number of premature births in the supplemented group was also statistically significant. In another study made in England and Wales by Balfour<sup>18</sup> 11,618 pregnant women chosen from the lowest income groups were fed a supplement of marmite or other yeast extract sufficient to furnish 240 I.U. of thiamine daily, or a proprietary preparation which furnished a rich supply of vitamins A and D, as well as calcium phosphorus and iron. Their controls were 8,095 pregnant women from the same area. The supplementary feeding resulted in a statistically significant reduction in the number of stillbirths and in the neonatal mortality rate.

In sum, then, whenever a relationship can be established between the incidence of prematurity and economic status, there would seem to be some reason to suspect dietary deficiencies as the cause; and, as already indicated, this seems to us a very probable explanation for the findings in regard to economic status presented in the present study.

#### FACTORS IN PREMATURE MORTALITY

The most important factor in premature mortality, of course, is the degree of prematurity as reflected fairly accurately by the weight of the infant. As may be seen in Table 12, approximately 65 per cent of our 3,331 prematures fell into the largest weight group (2,000-2,499 Gm.), about 25 per cent belonged to the middle category (1,500-1,999 Gm.), while some 10 per cent fell into the smallest group (1,000-1,499 Gm.). The mortality percentages in the three weight groups showed, in rough fashion, an inverse relationship to the frequency with which infants in these three cate-

TABLE 12  
*Total Infant Mortality*

INFANT WEIGHT	INFANTS	% OF TOTAL PREMATURES	DEATHS	%
2,500+ Gm.	25,162		745	3.0
2,000-2,499 Gm.	2,155	64.7	243	11.3
1,500-1,999 Gm.	792	23.8	287	36.2
1,000-1,499 Gm.	384	11.5	272	70.8
Total prematures	3,331	100.0	802	24.1

gories were encountered with the result that the absolute number of babies lost in each group was of the same order. This curious interrelationship makes possible the following general deduction: any inroads which can be made on mortality rates in any of these weight groups, if of similar degree, will salvage a similar number of babies despite the widely different sizes of the groups. To make this point clear let us suppose that, by some miracle, all the mortality rates given for prematures in Table 12 could be reduced by one-half; the resultant saving in the 3 groups from above downward would be 121, 143 and 136.

The outcome for our infants in all weight categories has improved decidedly in recent years as may be seen in Tables 13 and 14. The mortality of full term infants has been reduced by one-half, while the death rate of the premature group as a whole has fallen from 28.4 per cent in the first ten-year period to 18.7 per cent during the last five years. All figures are uncorrected.

In an effort to inquire into the factors responsible for this improvement, the deaths have been divided into three main groups: (1) stillbirths (died in utero or failed to respire after birth); (2) deaths during the first 24 hours of life (respiration having occurred); and

(3) deaths subsequent to the first day. The findings are given in Table 15. Here it may be seen that approximately one-half our deaths in premature infants occurred as stillbirths; about one-quarter took place within the first 24 hours (first day) of life; while another one-quarter, roughly, occurred later. These findings are important by way of showing that death in utero and the first day loom extremely large in total premature mortality. In the stillbirth group, premature separation of the placenta, placenta previa and one or another form of toxemia, were responsible for the majority of the fatalities.

Table 16 presents our infant mortality rates during the past five-year period, according to time of death. A comparison of this table with Table 15 will show that the most outstanding improvements in premature mortality rates have occurred in two categories. In the first place, stillbirths in the 2,000-2,499 Gm. group have fallen from 6.4 per cent, for the 20-year period as a whole, to 3.9 per cent in the last five years. In the second place, neonatal deaths after the first day in the 1,500-1,999 Gm. group have fallen from 7.7 per cent for the 20-year period as a whole to 4.2 per cent in the last five years. This marked reduction in the stillbirth rate among the 2,000-2,499 Gm. group is presumably the result of better obstetric management of these labors. Plausibility is lent to this surmise by the fact that a similar improvement was observed in the stillbirth rates among our mature babies—a fall from 2.2 per cent for the 20-year period as a whole to 1.5 in the last five years. The factors which, in our opinion, are responsible for these lowered stillbirth rates will be discussed in the last section of this paper.

TABLE 13  
*Infant Mortality in Two Ten-Year Periods*

INFANT WEIGHT	1926-1936			1936-1945		
	INFANTS	DEATHS	%	INFANTS	DEATHS	%
2,500+ Gm.	10,491	437	4.2	14,671	308	2.1
2,000-2,499 Gm.	905	135	14.9	1,250	108	8.6
1,500-1,999 Gm.	356	147	41.3	436	140	32.1
1,000-1,499 Gm.	153	119	77.8	231	153	66.2
Total prematures	1,414	401	28.4	1,917	401	20.9

TABLE 14  
*Infant Mortality in Last Two Five-Year Periods*

INFANT WEIGHT	JUNE 1, 1936-DECEMBER 31, 1940			JANUARY 1, 1941-DECEMBER 31, 1945		
	INFANTS	DEATHS	%	INFANTS	DEATHS	%
2,500+ Gm.	6,167	146	2.4	8,504	162	1.9
2,000-2,499 Gm.	515	49	9.5	735	59	8.0
1,500-1,999 Gm.	198	70	35.4	238	70	29.4
1,000-1,499 Gm.	112	78	69.6	119	75	63.0
Total prematures	825	197	23.9	1,092	204	18.7



TABLE 15  
*Infant Mortality by Time of Death*  
(1926-1946)

INFANT WEIGHT	INFANTS	TOTAL DEATHS		STILLBIRTHS		DIED FIRST DAY		DIED LATER	
		DEATHS	%	DEATHS	%	DEATHS	%	DEATHS	%
2,500+ Gm.	25,162	745	2.9	568	2.3	64	0.25	113	0.45
2,000-2,499 Gm.	2,155	243	11.3	137	6.4	48	2.2	58	2.7
1,500-1,999 Gm.	792	287	36.2	141	17.8	85	10.7	61	7.7
1,000-1,499 Gm.	384	272	70.8	113	29.4	99	25.8	60	15.6
Total prematures	3,331	802	24.1	391	11.7	232	7.0	179	5.4

TABLE 16  
*Infant Mortality by Time of Death*  
January 1, 1941 to December 31, 1945

INFANT WEIGHT	TOTAL FOR PERIOD			STILLBIRTHS		DIED FIRST DAY		DIED LATER	
	INFANTS	DEATHS	%	DEATHS	%	DEATHS	%	DEATHS	%
2,500+ Gm.	8,504	162	1.9	126	1.5	17	0.2	19	0.2
2,000-2,499 Gm.	735	59	8.0	29	3.9	14	1.9	16	2.2
1,500-1,999 Gm.	238	70	29.4	36	15.1	24	10.1	10	4.2
1,000-1,499 Gm.	119	75	63.0	33	27.7	26	21.8	16	13.4
Total prematures	1,092	204	18.7	98	9.0	64	5.9	42	3.8

The marked improvement in neonatal deaths occurring after the first day in the 1,500-1,999 Gm. group, is chiefly the result of the meticulous care which these infants have received by our Department of Pediatrics. Since this is a pediatric problem it will not concern us here except for one observation. It would seem logical to believe that improved pediatric care of premature infants will reap its greatest reward in 1,500-1,999 Gm. babies who have survived the first day. Infants between 2,000 and 2,499 Gm. are sufficiently mature, as a rule, to do rather satisfactorily with suboptimal care; while, at the other extreme, infants in the 1,000-1,499 Gm. group are so often handicapped by extremely immature organs that even the best attention often proves futile. In this group between, however, the degree of development is such that—given all the refinements of modern pediatric care, both medical and nursing—the outlook for survival is good; but with inadequate care, it is poor. For this group, then, more so than for the other two, perhaps, environment becomes the determining factor in survival.

Once a premature baby is born alive, obstetrician and pediatrician alike are confronted with the problem of prognosis. This will naturally depend not only on its weight but on the clinical picture presented by the individual infant: the degree of cyanosis with and without oxygen, the character of the respirations, the turgor of the skin, the way it takes food, etc. Nevertheless, prognoses based upon average figures are always helpful guides and to this end, Table 17 has been prepared by eliminating stillbirths

from Tables 15 and 16. Here is tabulated what we found to be the outlook, according to weight, for infants born alive and first-day survivors, both for the entire 20-year interval and for the last five-year period. This table shows among other things the striking improvement in prognosis which the smaller premature infants enjoy if they survive the first day. Thus, for the last five-year period, the percentage likelihood of death falls after the first 24 hours from 16.8 to 5.6 per cent in the 1,500-1,999 Gm. category, and from 48.9 to 26.7 per cent in the 1,000-1,499 Gm. group. (In evaluating Table 17 it should be recalled that all the infants reported in this paper were born in the hospital and that these figures would not necessarily apply to premature infants born in the home and later brought to a premature center.)

Table 18 shows that the mortality rates for white and negro prematures are about the same, as already noted. It has long been realized that female prematures of the same weight have a somewhat better outlook than males, as is brought out in Table 19. Female infants, of course, at all gestational ages tend to be smaller than the male so that a given female premature weighing the same as a given male premature is actually more mature, as a rule, from the viewpoint of gestational age. This is probably the explanation, in part at least, for this difference.

#### HOW BETTER OBSTETRICS CAN LOWER PREMATURE MORTALITY

On the basis of the above study plus general clinical experience it is believed that premature mortal-

TABLE 17

*Prognosis of Infants Born Alive and of First-Day Survivors in Various Weight Groups*  
(By "infants born alive" is meant babies who exhibit respiration after birth)  
1926-1941

INFANT WEIGHT	BORN ALIVE			FIRST-DAY SURVIVORS		
	INFANTS	DEATHS	%	INFANTS	DEATHS	%
2,500+ Gm.	24,594	177	0.7	24,530	113	0.5
2,000-2,499 Gm.	2,018	106	5.3	1,970	58	2.9
1,500-1,999 Gm.	651	146	22.4	566	61	10.8
1,000-1,499 Gm.	271	159	58.7	172	60	34.9

January 1, 1941-December 31, 1945

2,500+ Gm.	8,378	36	0.4	8,361	19	0.2
2,000-2,499 Gm.	706	30	4.2	692	16	2.3
1,500-1,999 Gm.	202	34	16.8	178	10	5.6
1,000-1,499 Gm.	86	42	48.8	60	16	26.7

TABLE 18

*Infant Mortality by Race*

INFANT WEIGHT	INFANTS	WHITE		INFANTS	NEGRO	
		DEATHS	%		DEATHS	%
2,500+ Gm.	14,231	324	2.3	10,931	421	3.9
2,000-2,499 Gm.	847	103	12.2	1,308	140	10.7
1,500-1,999 Gm.	318	115	36.2	474	172	36.3
1,000-1,499 Gm.	151	114	75.5	233	158	67.8
Total prematures	1,316	332	25.2	2,015	470	23.3

TABLE 19

*Infant Mortality by Sex*

INFANT WEIGHT	INFANTS	MALE		INFANTS	FEMALE	
		DEATHS	%		DEATHS	%
2,500+ Gm.	13,018	431	3.3	12,144	314	2.6
2,000-2,499 Gm.	1,013	132	13.0	1,142	111	9.7
1,500-1,999 Gm.	423	179	42.3	369	108	29.3
1,000-1,499 Gm.	200	151	75.5	184	121	65.8

ity could be lowered substantially if practitioners of obstetrics would act on the following suggestions:

1. Expectant mothers everywhere should be apprised of the desirability of an amplified diet in respect to minerals, proteins and vitamins. Although the role of nutritional deficiency in the etiology of premature birth does not lend itself to absolute proof, the evidence presented in this paper, original and otherwise, can leave little doubt that poor diet is probably the most common cause of this complication. At the risk of belaboring a well-known point, let it be re-emphasized that pills and capsules are no substitutes for the minerals and vitamins found in natural foods and that the daily menu of every pregnant woman should contain liberal amounts of milk, meat, green and yellow leafy vegetables, citrus fruits and whole wheat bread and cereals. Surely, this preventive approach to the premature problem promises to yield far more in terms of infants saved than all the refinements of pediatric therapy can possibly achieve. In this connection it will be instructive to

recall that the outlook for a full-term baby born alive is ten times better than a premature baby even though the latter belongs to the most favorable weight group (Table 17).

2. Vitamin K should be administered to all women as soon as labor starts. This statement is made with full realization of the skepticism with which some obstetricians regard this procedure. However, our Baltimore experience, now extending over some eight years, affords proof positive that in this community, at least, hemorrhagic disease of the newborn is relatively common and can be prevented by the antepartum administration of vitamin K. It is my opinion, moreover, that our dramatically lowered mortality rates during recent years, both for mature and premature infants, are in part attributable to this routine.

3. Although the obstetrician must be wary, it seems likely that certain cases of placenta previa and some patients with mild pre-eclampsia might be carried nearer to term than has heretofore been customary

and this without increased risk to the mother. If patients can be brought to within five weeks of term, the outlook for an easily viable, approximately 2,200-Gm. baby is good.

4. Patients who rupture their membranes prematurely should be left alone, preferably in the hospital, and no attempt made to bring on labor. They will often go for weeks with ruptured membranes and finally go into labor near term without event. The chief potential danger is intra-uterine infection, especially if coitus should take place. If all possibility of the latter can be eliminated, the patient can stay at home. We have handled at least 100 cases of premature rupture of the membranes in this manner without complication, but now and then, especially in negroes, penicillin may be necessary because of infection. Years ago we used to rush in and induce labor in these cases; however, we got into no end of maternal difficulties by so doing, and in addition lost many infants from prematurity. It is now widely recognized that interference is rarely necessary in these cases.

5. Patients in premature labor should be permitted no form of analgesia except continuous caudal or spinal anesthesia. We have found continuous caudal ideal.

6. Likewise, the delivery should be effected by caudal, spinal or local infiltration anesthesia.

7. Delivery should be preceded by a liberal median episiotomy.

8. In my opinion, the best way to effect delivery of a premature infant—especially a small one—is as follows: with the head on the perineum and the vulvar ring just beginning to distend, a median episiotomy is made and this is followed by gentle fundal pressure. This usually suffices for most cases but with some of the larger prematures, gentle forceps extraction may be advisable. When possible we prefer spontaneous delivery, assisted by fundal pressure, to forceps. In this connection, it should be noted that statistical studies of forceps vs. spontaneous delivery in premature labors are subject to an inherent error because it is the larger babies—those with the better prognosis because of gestational age and size—which most often call for forceps extraction. Obviously, therefore, most forceps series are weighted with the larger babies and hence tend to show “statistically” better results, but ones which we know are misleading for the reason stated.

9. The cord should not be clamped until pulsations cease since these infants, due to their tendency to develop anemia, need all the blood they can get.

10. The infant now becomes a pediatric problem,

but it should be remembered by obstetricians as well as pediatricians that the main immediate desiderata are: a clear airway, oxygen, warmth and as little handling as possible.

## BIBLIOGRAPHY

1. Brown, E. W., R. A. Lyon, and N. A. Anderson: Causes of prematurity. VI. Influence of toxemia on the incidence of prematurity, *Am. J. Dis. Child.*, 71:378, 1946.
2. Anderson, N. A., and R. A. Lyon: Causes of prematurity. I. Review of the literature, *Am. J. Dis. Child.*, 58:586, 1939.
3. McCance, R. A., E. M. Widdowson, and C. M. Verdon-Roe: A study of English diets by the individual methods: III. Pregnant women at different economic levels, *J. Hygiene*, 38:596, 1938.
4. Hart, E. B., H. Steenbock, and G. C. Humphrey: The influence of rations restricted to the oat plant on reproduction in cattle, *Research Bull. No. 49*, Wisc. Agri. Exp. Sta., 1920.
5. Smith, G. E.: Fetal athyrosis, *J. Biol. Chem.*, 29:215, 217.
6. Hale, F.: The relation of maternal vitamin A deficiency to microphthalmia in pigs, *Texas State J. Med.*, 33:228, 1937.
7. Warkany, J., and R. C. Nelson: Congenital malformations induced in rats by maternal nutritional deficiency, *J. Nutrition*, 23:321, 1942.
8. Maxwell, J. P., H. T. Pi, H. A. C. Lin, and C. C. Kuo: Further studies in adult rickets (osteomalacia) and fetal rickets, *Proc. Roy. Soc. Med.*, 32:287, 1939.
9. Toverud, G.: Preventive dentistry in the pre-school period and particularly during foetal life, *Dental Magazine & Oral Topics*, 55:299, 1938.
10. Burke, Bertha S.: Study of the nutrition of groups of children selected on the basis of no defective deciduous teeth and high incidence of deciduous teeth, *Child Development*, 11:327, 1940.
11. Teel, H. M., B. S. Burke, and R. Draper: Vitamin C in human pregnancy and lactation. I. Studies during pregnancy, *Am. J. Dis. Child.*, 56:1004, 1938.
12. Ebbs, J. H., F. F. Tisdall, and W. A. Scott: The influence of prenatal diet on the mother and child, *J. Nutrition*, 22:515, 1941.
13. Ebbs, J. H., W. A. Scott, F. F. Tisdall, W. J. Moyle, and M. Bell: Nutrition in pregnancy, *Canad. M. A. J.*, 46:1, 1942.
14. Ebbs, J. H., A. Brown, F. F. Tisdall, W. J. Moyle, and M. Bell: The influence of improved prenatal nutrition upon the infant, *Canad. M. A. J.*, 46:6, 1942.
15. Ebbs, J. H.: Nutritive requirements in pregnancy (review), *J. A. M. A.*, 121:339, 1943.
16. Burke, Bertha S., V. A. Beal, S. B. Kirkwood, and H. C. Stuart: The influence of nutrition during pregnancy upon the condition of the infant at birth, *J. Nutrition*, 26:569, 1943.
17. Interim report of the People's League of Health: Nutrition of expectant and nursing mothers, *Lancet*, 2:10, 1942.
18. Balfour, M. I.: Supplementary feeding in pregnancy, *Lancet*, 1:208, 1944.

# The Role of Vitamin Deficiencies in Neuropsychiatric Diseases\*

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*This article describes the neuropsychiatric symptoms and diseases which at present seem to be quite clearly associated with vitamin deficiencies in man. The author has conservatively restricted the discussion to those conditions for which the evidence of relationship of the disease to vitamin deficiency is reasonably well established. Even in these instances, however, the symptoms and signs are rarely specific, and as the author has shown so well, some evidence of an actual vitamin deficiency, such as clearly deficient dietary intake, is needed in addition to the presence of symptoms and response to a therapeutic trial before vitamin deficiency can be diagnosed with reasonable accuracy.*

There are certain generalities which should be borne in mind when considering vitamin requirements and deficiencies in man.

First, vitamin requirements vary from one individual to another, so that what may be adequate for one person may over a period of time cause a vitamin deficiency in a person with a higher requirement.

Secondly, some conditions cause an increase in vitamin requirements. An increased basal metabolic rate is associated with an increased need for vitamin B, as is vomiting or diarrhea or any dysfunction of the gastro-intestinal tract, chronic wasting illnesses such as tuberculosis, diabetes, liver disease, and chronic alcoholism.

Thirdly, the rate of excretion of vitamins varies from one individual to another.

Fourthly, human beings, as contrasted with experimental animals, are more likely to have multiple rather than single deficiencies. This is especially true of vitamin B deficiencies since natural foods almost without exception contain members of the vitamin B group in combination rather than singly.

## VITAMIN A

Vitamin A seems to be unimportant in central nervous system metabolism. Its importance arises from

the fact that if a vitamin A deficiency is present in early life, there may be a disproportionate growth of the central nervous system in relation to the bone around it. (Vitamin A is important for growth.) Skeletal growth becomes retarded before the other tissues and mechanical damage can be done to the brain and spinal cord.

## VITAMIN B

The vitamin B group seems to have most to do with the nervous system. Of this complex of vitamins, vitamin B<sub>1</sub> and nicotinic acid seem to be intimately related to nervous system metabolism, especially B<sub>1</sub>. Carbohydrate is the chief foodstuff of the brain and B<sub>1</sub> plays an important role in its metabolism, facilitating the oxidation of pyruvic acid. When there is a deficiency of B<sub>1</sub> there is interference with nervous system metabolism and function.

### PATHOLOGY OF VITAMIN B DEFICIENCIES

If this interference in nervous system metabolism is severe, demonstrable changes in the nervous system are produced. The *peripheral nerves* are most commonly affected. First, there is demyelination of the nerve fibers and later destruction of the axis cylinders. In general the nerves of the lower extremities are involved first, and sensory impairment is generally greater than motor involvement. If the nerve degeneration is severe, it may not be reversible.

Changes may also be produced in the *spinal cord*. Regardless of the cause of the vitamin B deficiency, a certain small percentage of patients with peripheral neuropathies develop demyelinating lesions of the spinal cord. As a rule the posterior columns alone are involved and quite characteristically, the columns of Goll more often than those of Burdack. As in the peripheral nerves, first there is destruction of the myelin sheaths and later of the axis cylinders. Involvement of the posterior columns is preceded by demyelination of the posterior nerve roots and this in turn is preceded by involvement of the peripheral nerves.

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In a certain number of instances other tracts may show involvement—the lateral and anterior pyramidal tracts and the lateral sensory columns. It is quite possible to get a picture of combined system disease which clinically is not associated with glossitis, achlorhydria or macrocytic anemia.

The spinal cord lesions resulting from vitamin B deficiency may resemble those seen in *tabes dorsalis* and it was this which led to the use of vitamin B for relief of pain in *tabes* (v.i.). Occasionally anterior horn cell changes too are seen in avitaminotic, malnourished, emaciated individuals.

**Brain.** In connection with severe vitamin B deficiencies (but possibly due to causes other than the  $B_1$  deficiency) there develops a hemorrhagic pseudo-encephalitis, which was first described by Wernicke. In the gray matter around the third ventricle, the aqueduct, and the floor of the fourth ventricle, and in the mamillary bodies and corpora quadrigemina, the capillaries become dilated and congested and have a tendency to rupture and produce "ring" hemorrhages. This is often associated with some perivascular cellular reaction and followed by proliferation of the capillary endothelium.

It is believed that the optic nerves may be involved in severe deficiencies. This was seen in a small number of American soldiers who were liberated from the Japanese after long imprisonment and starvation.

#### CLINICAL ASPECTS OF VITAMIN $B_1$ DEFICIENCIES

**Polyneuropathy.** The onset is generally insidious, with heaviness of the legs and tenderness of the calf muscles. Weakness may not be apparent except after a long walk, at times as much as a mile. There is burning of the soles and numbness of the dorsum of the feet, weakness of dorsi flexion of the toes, diminished tendon reflexes, and progressive motor and sensory impairment. Vibratory sensation is usually lost early and it may be the last to reappear. If treated early, before irreversible changes have taken place in the nerves, response to intensive therapy with  $B_1$  is very successful. The same generalization applies to spinal cord involvement.

Wernicke's syndrome (hemorrhagic pseudo-encephalitis) which is seen in alcoholics, pellagrins, pernicious vomiting of pregnancy, and with gastro-intestinal malignancies associated with cachexia and vomiting, is characterized by clouding of consciousness, ocular muscle palsies, and ataxia; it is usually preceded by delirium. The eye-muscle paralyses, and the mental symptoms usually improve with thiamin therapy. Because it is thought that vitamin  $B_1$  deficiency is

not the only cause, multiple vitamin treatment is recommended for this condition. In cases which recover with vitamin therapy, it is not unusual for a Korsakoff's syndrome to develop.

#### RELATIONSHIP BETWEEN VITAMIN $B_1$ DEFICIENCY AND PSYCHIATRIC DISORDERS

There have been several studies which have demonstrated convincingly that such a relationship exists. Dr. Ray D. Williams<sup>1-3</sup> and his co-workers induced pure vitamin B deficiencies in a group of female patients in a Minnesota state hospital. They were patients who had recovered from acute phases of their psychiatric illnesses. The experiment was carefully controlled and the observations seem valid despite the fact that state hospital patients were used.

In general, the more active patients revealed some evidence of abnormality within four weeks of the time they were placed on the special diet. In all of the cases clear evidence of psychologic disturbances appeared before the end of 12 weeks, such as changes in behavior, marked alteration of attitude and progressively decreasing ability to perform accustomed tasks or to make social adjustments within the group. All of the subjects became irritable, depressed, quarrelsome, unco-operative and fearful. Without knowing why, they thought some calamity awaited them. Two became agitated and threatened suicide. All developed generalized weakness, inability to concentrate, confusion of thought, and impairment of memory. There were frequent minor accidents and much breaking of equipment. These symptoms had not been present before, and they disappeared after the administration of thiamine which was given without the knowledge of the patients.

There were other symptoms observed in this group of patients on a vitamin  $B_1$  deficient diet: Headache, backache, painful menstrual periods, insomnia, tension, paresthesias and hypersensitivity to painful stimuli and noise. It might be stated that the patients had been selected because they were noncomplainers. Loss of appetite with episodes of nausea and vomiting developed in all cases and epigastric distress after meals was a frequent complaint.

Another study of importance was that of Spies and his co-workers.<sup>4</sup> They studied over 1,700 patients attending the Nutrition Clinic of the Hillman Hospital in Birmingham, Alabama. At some time or other most of these patients complained of mental disturbances which waxed and waned with the seasons. They selected 115 patients without beriberi but whose diets were low in thiamine. After being given injec-

tions of saline first they were given 50 mg. of thiamine. Hundreds of similar patients were used as controls.

Prior to the administration of thiamine the emotional abnormalities most frequently encountered were fear, apprehension, irritability, anger, hostility, depression, extreme sensitivity and emotional instability. Many patients presented pictures of anxiety states and phobic reactions. Many expressed pseudo-hallucinations. Practically all of them complained of poor memory which may have been due to difficulty in concentrating.

The intravenous injections of 50 mg. of thiamine produced a truly amazing change in personalities within from 30 minutes to 20 hours: a transformation from a timid, apprehensive, shrinking, fearful, depressed, unreasonable, unco-operative person to a smiling, pleasant, friendly, co-operative, happy human being. Every patient in whom there was conclusive evidence of deficiency disease with emotional disturbances showed an improvement or disappearance of symptoms following thiamine treatment. In many instances saline injections were given prior to the giving of B<sub>1</sub> to see if the results were due to suggestion, but in no case was there similar improvement after the injection of saline.

Spies concluded that various emotional disturbances and vague symptoms, either physical or mental, may be the only evidence of altered bodily function arising from a vitamin B<sub>1</sub> deficiency state. It was his feeling that those mild mental disorders of deficiency states were frequently considered to be true psychoneurotic disorders. He by no means advocated that all types of psychoneurotic disorders be treated by vitamins. However, when they are associated with *deficiency diseases* or *known defective diets* vitamin therapy should be given first.

A third study along the same lines was done by Jolliffe and his co-workers at Bellevue Hospital.<sup>5</sup> Five of the hospital medical staff co-operated with them by remaining on a carefully figured diet deficient in vitamin B<sub>1</sub>. Neuropsychiatric syndromes were produced in four out of the five subjects. They complained of fatigue, lassitude, anorexia, precordial pain, burning of the feet, dyspnea on exertion, muscle cramps and palpitation. Symptoms appeared as early as the fourth day, and the addition of thiamine alone to the experimental diet caused all symptoms to disappear within three days.

With proper precaution Jolliffe warned that it should not be inferred that all neurasthenia is based on thiamine or other nutritional deficiency. It seemed fairly clear to him, however, that a syndrome

possessing many of its characteristics could be produced by a nutritional deficiency.

It should be borne in mind that these studies should not be made the basis for considering vitamins as a panacea for emotional disturbances. The possibility of a B complex deficiency state should be kept in mind when suspicious and uncertain mental and neurologic symptoms are present *in the presence of a deficient diet or disease which interferes with the absorption or utilization of vitamins*. The usual poly-vitamin pills are not suitable for therapeutic use in patients with such clinical deficiencies. Larger doses must be used, and in some instances parenterally.

#### NICOTINIC ACID DEFICIENCY

That mental symptoms are associated with pellagra is well known. In some instances the mental symptoms may appear before the other signs of pellagra are evident. Those who have studied pellagra have recognized early emotional manifestations which in many respects resemble those seen in vitamin B<sub>1</sub> deficiency states, and which may as a matter of fact be related to a coexisting but unrecognized B<sub>1</sub> deficiency. A patient with a typical pellagra psychosis, however, presents a picture of severe impairment of memory, disorientation, confusion, confabulation and either manic depressive or paranoid reaction. In the early cases the psychosis responds rapidly to treatment with nicotinic acid but as with vitamin B<sub>1</sub> disorders, if the psychosis is long standing irreversible changes may be produced and no response be obtained from treatment.

Other psychiatric syndromes due to nicotinic acid deficiency have been described. Jolliffe and his co-workers<sup>6</sup> have described what they have called nicotinic acid deficiency encephalopathy in which the outstanding symptoms are sucking and grasping reflexes, changing cogwheel rigidities, and progressive clouding of consciousness. They reported 150 cases with reduction in mortality from above 90 per cent to 15 per cent, with nicotinic acid treatment.

Cleckley, Sydenstricker and Geeslin<sup>7</sup> have reported severe psychotic reactions without any evidence of pellagra which responded to nicotinic acid. Their cases presented a picture of toxic psychosis or delirium with excitement, delusions, hallucinations and disorientation. Most of these patients were old patients and much larger doses of nicotinic acid were required than in the treatment of pellagra.

Delirium tremens<sup>8</sup> is another psychiatric syndrome which seems to be related to vitamin B deficiency. Patients with delirium tremens generally give a his-

tory of dietary inadequacy. They may show low vitamin C contents in their blood and spinal fluid. About 30 per cent of them show peripheral neuropathies and often there is an associated pellagra, scurvy or riboflavin deficiency. They are generally obviously dehydrated, blood chlorides are practically always found to be low, and spinal fluid pressure was not found to be increased by Bowman and his co-workers. This is quite important since in the past patients with delirium tremens were thought to have "wet brains" and were treated accordingly. Since the recognition of the role of vitamin deficiencies in delirium tremens, most places have adopted a plan of treatment which involves the administration of salt and fluids, carbohydrates, small amounts of insulin and high caloric and vitamin rich diets supplemented by additions of B complex and vitamin C.

Korsakoff's syndrome is another psychiatric disorder which is now thought to be associated with vitamin B deficiency. While it is most commonly seen in chronic alcoholics, it also occurs in connection with head injuries, diabetes, arteriosclerosis, subarachnoid bleeding and toxic and drug psychoses. The outstanding symptoms are defective memory for recent events, tendency to confabulate, disorientation for time, place and person. The presence of peripheral neuropathy completes the picture. Thiamin treatment appears to be of value in cases of acute onset when given early. In chronic cases results have been discouraging. It may be that in chronic cases irreversible changes in the cortex have taken place.

#### OTHER B COMPLEX VITAMINS

Riboflavin deficiency is not known to cause any mental or neurologic symptoms in man.

Of the remainder of vitamins in the B complex group, only one is believed to have any connection with the nervous system metabolism and that is *pyridoxine* or *vitamin B<sub>6</sub>*. Pyridoxine was used by Jolliffe in parkinsonism. Fifteen chair or bedfast patients were given 50 to 100 mg. daily for four weeks with some improvement in four patients. Other workers who have repeated this work have described no effect.

Vitamin B<sub>1</sub> has been used with some success in relieving the pain of *tabes dorsalis*. Intraspinal injections of 50 to 100 mg. produced relief from pain for several weeks or several months in some patients. The results seemed to be better maintained when vitamin B complex was given concurrently by mouth or intramuscular injection.

#### VITAMINS C AND D

Vitamin C and D are not known to produce nervous system disorders.

#### VITAMIN E

Most of the knowledge concerning the effects of vitamin E deficiency has been derived from experimental work with animals. In 1928 Evans and Burr<sup>8</sup> found that the offspring of female rats who were deficient in vitamin E often became completely paralyzed toward the end of lactation. This was later shown to be due to an intense and selective necrosis of skeletal muscles. There were no changes, however, in the central nervous system of rats on vitamin E deficient diets. These findings suggested the possibility that muscular dystrophy in man was due to vitamin E deficiency.

There is no exact knowledge of the quantitative vitamin E requirements for man. So far the therapeutic response of dystrophies to alpha tocopherol have been disappointing. It is possible, however, that the dystrophies are related to an inability of the patients to utilize tocopherol. In our present state of knowledge there would appear to be no harm in giving it a trial in patients with muscular dystrophies and atrophies.

#### BIBLIOGRAPHY

1. Williams, R. D., H. L. Mason, R. M. Wilder, and B. F. Smith: Observations on induced thiamin deficiency in man, *Arch. Int. Med.*, 66:785 (Oct.) 1940.
2. Williams, R. D., and H. L. Mason: Further observation on induced thiamin (vitamin B<sub>1</sub>) deficiency and thiamin requirement of man, *Proc. Staff Meet., Mayo Clin.*, 16:433-438, 1941.
3. Wilder, R. M.: Symptoms and signs of thiamin deficiency—Chap. IX, *The Role of Nutritional Deficiency in Nervous and Mental Disease*, Baltimore, Williams & Wilkins, 1943.
4. Spies, T. D., J. Bradley, M. Rosenbaum, and J. R. Knott: Emotional Disturbances in Persons with Pellagra, Beriberi and Associated Deficiency States, *Proc. A. Research Nerv. & Ment. Dis.*, 22: Chap. XI.
5. Jolliffe, N., R. Goodhart, J. Gennis, and J. K. Cline: The experimental production of vitamin B<sub>1</sub> deficiency in normal subjects, *Am. J. M. Sc.*, 198:198, 1939.
6. Jolliffe, N., K. M. Bowman, L. A. Rosenblum, and H. D. Fein: Nicotinic acid deficiency encephalopathy, *J. A. M. A.*, 114:307, 1940.
7. Cleckley, H. M., V. P. Sydenstricker, and L. E. Geeslin: Nicotinic acid in the treatment of atypical psychotic states, *J. A. M. A.*, 112:2107, 1939.
8. Evans, H. M., and G. O. Burr: On amount of vitamin B required during lactation, *J. Biol. Chem.*, 76:263 (Jan.) 1928.

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## Scientific Tests in Evidence

### Blood Grouping Tests in Disputed Paternity Cases

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The reference to disputed paternity cases makes the title unnecessarily restricted. "Blood grouping tests in cases of disputed parentage" would have been the more appropriate title, because the tests can be used equally well in cases of disputed maternity, and generally in cases of disputed parentage.

Problems of disputed parentage probably confronted mankind long before the days of recorded history. As a matter of fact nothing can illustrate better the advance made by the introduction of blood grouping tests than a comparison of two similar cases that occurred about 3,000 years apart.

The first case was one of disputed maternity. It is recorded in 1 Kings, Chapter 3, Verses 16 to 28. According to the record, King Solomon, confronted with two women claiming the same child, resorted to psychology and solved the case to everybody's satisfaction.

The second case, this time of disputed parentage, was solved in a different way.

It happened in Chicago in 1930, that Mrs. W. gave birth to a child in a hospital, and Mrs. B. gave birth to a child in the same hospital, on the same day. Both left the hospital with their children, again on the same day. When Mrs. W. came home, she found that her baby had a tag on its back with the letter "B." Mrs. B. found that the tag on the back of her baby had on it the letter "W." There was much confusion, much heartache and much publicity, until blood group experts were called in. They solved the problem promptly by means of blood grouping tests, which showed, beyond any doubt, that the baby brought home by Mrs. W. could not have been the child of Mrs. W., but could have been, very well, the child of Mrs. B.; and, vice versa, that the child brought home by Mrs. B. could not have possibly been the child of Mrs. B., but that it could very well

have been the child of Mrs. W. The babies were exchanged, and, as far as is known, both families have lived happily ever since.

Blood grouping tests are used in courts in connection with three types of legal procedure: (1) For exclusion of parentage, most frequently for exclusion of paternity; (2) for identification of fresh blood and of dried blood stains; (3) for identification of secretions, especially of sperm, in cases of rape. The present discussion will be limited to the use of blood grouping tests for determination of nonpaternity or for the exclusion of paternity.

Blood consists of formed elements, red blood cells and white blood cells, which are suspended in a liquid called plasma or serum. For the purpose of this discussion, the difference between plasma and serum is immaterial and the two terms will be used interchangeably.

When a drop of human blood is viewed through the microscope, it is found to consist of tiny biscuit-shaped disks evenly distributed in the liquid medium of plasma. When blood of two different persons is mixed, one of two things happens. In some instances the mixture retains the same appearance as the unmixed samples had, both to the naked eye and when viewed with the microscope. Such two bloods are compatible. In other cases, the mixture loses the normal, opaque, homogeneous appearance, large clumps can be seen with the naked eye, and under the microscope the clumps can be recognized as made up of masses of red cells which stick to each other as if glued by some invisible adhesive. The blood of such two persons is incompatible.

It was such an observation that led Karl Landsteiner to discover differences in the blood of man. He found the reason why in mixtures of blood of some persons, red cells stick to each other. There are two distinct and specific substances in red cells: A and B. They are known as blood factors and are the basis

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of the four so-called blood groups: group A, containing factor A, is present in about 40 per cent of the population; group B, containing factor B, present in about 13 per cent; group AB, containing both factors, A and B, present in about 5 per cent; and finally the most common group O, devoid of both A and B, present in about 42 per cent.

Corresponding with the factors in the red cells, there are substances in the plasma, known as agglutinins, which are responsible for the clumping. One agglutinin, opposed to A and called anti-A, clumps red cells with factor A, the other, opposed to B, or anti-B, clumps red cells with factor B. Clumping of red cells in the blood vessels during life, is dangerous, and, in extreme cases, even incompatible with life. Therefore, normally in the human body, the blood factors and the opposing agglutinins are never present in the blood of the same person. A person of group A does not have anti-A in his plasma, but only anti-B; accordingly, a person of group B does not have anti-B in his plasma, but anti-A; for the same reason, a person of group AB lacks in his plasma both anti-A and anti-B; finally, a person of group O, who lacks both factors, A and B, in his red cells, has both agglutinins, anti-A and anti-B, in his plasma.

The rules of blood grouping tests are simple and easily understood. As a matter of fact, they can be easily carried out in court.

Suppose we have to find to what group a person belongs. For it, we need two samples of plasma, one of a person of group A and the other of a person of group B. Plasma of a person of group A contains agglutinins against B, anti-B, plasma of a person of group B contains agglutinins anti-A. A drop of plasma of each kind is placed on a slide, separated from each other. A drop of blood, the group of which is unknown, is added to each of the two drops of plasma. One of four things will happen. If there is no clumping in either mixture, the inference is that the blood lacks factors A and B, and belongs to group O. If both mixtures show clumping, the blood belongs to group AB. If the mixture of the blood with the plasma containing anti-A shows clumping, but there is no clumping with the plasma containing anti-B, then the blood belongs to group A. Finally, if there is clumping in the mixture with plasma containing anti-B, but none with the plasma containing anti-A, the blood belongs to group B.

This is the basic procedure of all grouping tests, reduced to its essentials. The reagents differ according to the blood factors tested; there are all kinds of variations. There are many sources of error, which the expert has to master, but all the differences are merely

modification of pattern outlined in the preceding paragraph.

In 1927 two other factors were found in human blood. They were labeled with the letters M and N. Every person contains one of the two, or both together, thus permitting the recognition of three further varieties of blood, known as types M, N, and MN. M is present in about 30 per cent of the population, N in 20 per cent, and both together, MN, in about 50 per cent. These types are entirely independent of the groups A, B, AB and O. There is nobody whose red cells are devoid of both M and N, in sharp contrast to the A and B factors, which are absent in group O, or 42 per cent of the population. Another important difference between the factors A and B, on one hand, and M and N on the other, is that while there are, in normal human blood, agglutinins anti-A and anti-B, there are, in human blood, no such agglutinins against M and N. Therefore, mixtures of human blood having the factors M and N do not show clumping. To test the factors M and N, agglutinins have to be produced artificially in animals by special technic. Rabbits are used as source of reagents for detection of types M and N.

The basis for the use of blood grouping tests in suits involving the question of parentage is the fact that blood groups are inherited according to scientifically established and firm laws known as Mendel's laws of inheritance. These laws permit prediction of the possible blood groups of children if the groups of the parents are known, and they permit also prediction of the possible blood groups of the father if the groups of the mother and of the child are known.

#### RULES GOVERNING INHERITANCE OF BLOOD GROUPS

1. A child inherits always one, but never more than one blood factor from each parent.
2. *Factors A and B cannot be present in the blood of a child unless present in the blood of one or both parents.* This is the first law of inheritance of blood groups.
3. If a child inherits A from each parent, then it belongs to group A.
4. If a child inherits B from each parent, then it belongs to group B.
5. If a child inherits A from one parent and B from the other, then it belongs to group AB.
6. If a child inherits A from one parent, and O from the other, it belongs to group A, because the A factor is a dominant, inheritable factor, and as such it obscures the recessive group O. On the other hand, this child, when grown to maturity, may transmit to his children either A or O. That is how group O

may appear in a child though it does not appear in the blood of the parents. It is present in the blood of the parents, but we have at present no means of detecting the presence of such recessive O group except by the absence of A and B.

7. Similarly, if a child inherits B from one parent and O from the other, it belongs to group B. Eventually such a child may transmit to its children either B or O.

8. *A person of group AB must transmit to his or her children factor A or B, and therefore cannot be the parent of a child of group O.* This is the second law of inheritance of blood groups.

9. *A person of group O cannot be the parent of a child of group AB, because a child of group AB must inherit the A from one parent and the B from the other, and a person of group O cannot possibly transmit the A or the B to his child.* This is the third law of inheritance.

10. *Factors M and N cannot appear in a child unless present in one or both parents.* This is the fourth law of inheritance.

11. *A parent M cannot have a child N, because a parent M transmits the M to his children, and cannot transmit N.* The fifth law of inheritance.

12. *Similarly, a parent N cannot have a child M.* The sixth law of inheritance.

The first, third, fourth, fifth and sixth laws of inheritance have been tested on tens of thousands of families by many competent investigators and found correct.

The second law of inheritance, the one stating that a parent of group AB cannot have a child O, was found to be correct in a similar number of families, but in one instance a mother of group AB had a child of group O. For that reason, it is recommended not to accept the results of an exclusion on the basis of the second law with the same finality as exclusions on the basis of the other five laws. Fortunately, only one in about 80 exclusions is based on the second law.

Exclusion of parentage on the basis of the other laws is considered to be absolutely reliable.

The most frequent occasion for the use of blood grouping tests is the situation which arises when a woman claims that a certain man is the father of her child and the man denies the charge. If the man is actually not the father, blood grouping tests are the only reliable scientific means available to prove his innocence. Tests have to be done on the blood of the mother, of the child, and of the putative father. If the examination includes tests for the factors A and B, M and N, it can show in approximately one-third of all cases of innocent but accused men that they cannot possibly be the fathers.

If the examination is limited to the simpler tests for the A and B factors, the chances of exclusion are only one in six. The chances of excluding paternity vary. They are inversely proportionate to the frequency of the man's blood group. For instance, a man with group AB, type N (the rarest combination) has 63.4 per cent chance of being excluded as possible father, if innocent, while a man with group A, type MN has only about 7.7 per cent chance.

Blood grouping tests can exclude paternity, but under ordinary circumstances cannot prove paternity. If a man cannot be excluded as a father, that does not mean that he is the father; any man with the same group could be the father. Therefore, the laws authorizing the use of grouping tests in cases of suits for paternity state specifically that if the result of the blood test fails to exclude paternity, it cannot be used as evidence against the defendant, because the test cannot be used for determination of paternity, but only for determination of nonpaternity.

**When the Mother's Blood Cannot Be Examined.** When the blood of the mother is not available for examination, paternity may still be excluded by examining the blood of the child and the putative father, though the chances are smaller than when the blood of all three is available. If the putative father belongs to group AB and the child to group O, or vice versa, nonpaternity is proved regardless of group of mother. Limiting the examination to the blood of the putative father and of the child may sometimes avert family trouble because if the putative father and the child belong to the same group, nonpaternity cannot be established regardless of the group of the mother.

It may be of interest to add that if the mother is telling the truth, namely, that the defendant is the only possible father, she may safely submit to the test. The result of the test cannot possibly be unfavorable for her, because it is not possible, under such circumstances, for the alleged father to become excluded as the possible father.

**Cases of Interchanged Babies.** Blood grouping tests in these cases must include parents of both children and the children. When A and B as well as M and N factors are examined, solution is possible in more than 40 per cent of cases.

#### ESSENTIAL FACTS

The application of blood grouping tests to legal procedure is based on the following facts:

1. The blood groups can be determined at birth or shortly thereafter. It is advisable to wait at least a month after the birth of a child before issuing an opinion regarding its blood group.

2. Blood groups are unchangeable and remain constant throughout life. They are not affected by disease, environment, and medication, regardless of whether given by mouth or by injection. They are independent of sex and age.

3. Blood grouping tests can be repeated as many times as is necessary by the same examiner or by another competent examiner. If done by qualified examiners, with the proper checks and controls, the results are reproducible.

There can be no doubt as to the dependability of blood grouping tests. There is absolute agreement of scientific authorities on that point. As a matter of fact, no authority of weight can be quoted adversely. Despite this consensus of scientific authority, judicial acceptance of the results of the tests has not been general or unanimous, even in states where laws have been enacted authorizing the use of blood grouping tests in cases of disputed paternity. None of the laws thus far enacted prescribes that exclusion of paternity by means of the test must be accorded decisive weight. All this is a matter of judicial concern. However, regardless of this attitude of the courts, it should be kept in mind that the result of an expertly done blood grouping test cannot be the subject of a controversy. Unlike other medical testimony, it cannot be the subject of varying interpretation by medical experts on either side. There cannot possibly be a difference of opinion about the results of the test based on application of the generally accepted laws of inheritance. By that I mean, that whereas there can be differences of opinion regarding the validity of the second law of inheritance, there can be no such difference regarding the other five laws, which form the basis of over 90 per cent of exclusions. No two experts can honestly express different opinions. The qualified expert who reports an exclusion of paternity is not expressing an opinion, but testifying to a scientific fact.

The tests can be carried out in the court room, in the presence of judges and jury. The results are easily interpreted and the interpretation can be made clear to any person. The results can be photographed and made a permanent part of the record. Therefore the medical investigator is in full agreement with the conclusions in 25 Iowa Law-Review 823: ‡

"The uncontradicted testimony of the expert negating paternity should be final. If it is doubted, other experts could take new tests until the facts of the blood content could be shown with accuracy. Then, where this was established, but one result would be scientifically possible, and for a court to hold to the contrary seems an absurdity."

It is reasonable to expect that the present chances of proving the innocence of men accused of paternity will be increased by advances of our knowledge of blood group factors. Even now, a recently discovered factor known as the Rh factor has added two per cent chances of exclusion and is likely to add more when further progress is made in the study of inheritance of so-called subgroups of the Rh factor.

The States of New York, Ohio, New Jersey, Wisconsin, Maryland, Maine, and South Dakota have laws giving courts in those states power to compel individuals involved in paternity suits to submit to blood-grouping tests. It is hoped that other states will have similar laws passed in the future. Such laws are the only means of protecting many innocent but accused men against unjust claims. There is little doubt that due to the failure to use blood-grouping tests more men may be paying alimony for other men's children than would be the case if blood-grouping tests were used in all cases in which the question of paternity is involved.

‡ No. 4 (May) 1940. See: Britt: Blood grouping tests and the law, 21 Minn. Law Review, 671, 693, 1937; 16 Indiana Law Journal, 408-411 (April) 1941.

## Chemical Tests for Alcoholic Intoxication

CLARENCE MUEHLBERGER, § PH.D.

I want to talk to you for a few minutes on the chemical tests for alcoholic intoxication. In a world which is rapidly becoming smaller and more complex, citizens are required to demonstrate an ever-increasing concern for their mutual welfare if chaos is not to ensue. Doubtless many of you can recall the day

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when the making of a 40-mile journey over country roads, even with a good team of horses, was a day's undertaking. Now, a half-century later, the same distance could be covered in 400 seconds, using our fastest jet-propelled plane. No small part of the unrest and uncertainty of our day stems from man's failure to keep pace socially with his rapidly developing-physical world.

The problems presented by the unwise use of alcoholic beverages are illustrative. In the days of our grandparents, if John Citizen hitched up the team, drove to the town tavern and imbibed too freely, no great danger resulted. He was assisted to his buggy, the horses headed in a homeward direction and he awakened later, safe in his own farmyard.

Today it is much different. Even a few stiff highballs or a few bottles of beer may create a serious hazard on the highway, regardless of whether our John Citizen is a pedestrian or the driver of an automobile. For the alertness, soundness of judgment and quickness of response required by our present traffic conditions is infinitely greater than it was in the horse-and-buggy days of our forefathers. All one needs to do is to look at the records of highway accidents in order to evaluate the seriousness of the situation. Casualties comparable to those of a two-front war are being rolled up daily on our highways. It seems imperative that such needless maiming and slaughter be stopped.

Now, I would be the last to attribute this alarming situation solely to John Barleycorn. Unquestionably a great many highway accidents are due to such factors as excessive speed, fatigue, poor visibility, unfortunate highway conditions, and the like. But studies in various parts of the country all indicate that in from 15 to 30 per cent of the accidents on our highways, the immoderate use of alcohol is a contributing factor. And in all too many instance, persons who are injured or killed are those innocent of any wrongdoing. Thus, in the interest of justice it frequently is of the utmost importance to determine as accurately as possible the extent to which alcohol was responsible for a person's impairment of function.

From the purely physiologic or medical point of view, the accurate diagnosis of alcohol-influence poses a difficult problem. There are so many other conditions which simulate alcoholic intoxication. The mere fact that a person has the odor of alcoholic liquor on his breath is no indication of intoxication; it merely shows that some alcoholic beverage has been swallowed. Likewise the other cardinal indications which have generally been thought to indicate intoxication are inaccurate. Uncertainty of step and slurring of speech, which are both referable to muscular inco-ordination, may result from conditions other than alcohol-influence. The ability to walk a chalk line certainly is a very poor quantitative index of a person's condition of sobriety or intoxication. Thus, if compelled to rely solely upon his observations and physical findings, even the most highly skilled physician might well be in a quandary as to the diagnosis of acute alcoholic intoxication.

Fortunately, medical science has provided excellent reliable objective techniques which can remove the diagnostic uncertainty of the purely physical observations. These tests, based upon the concentration of alcohol which is circulating in the body of the subject, involve the chemical analysis of blood, urine, saliva, or breath. Whether or not these may be legally demanded, or taken under protest, is a matter which I would like to leave for Professor Inbau's consideration. I will therefore restrict my comments to the reliability and degree of medical certainty of the tests.

In explaining these chemical tests, it might be well to mention some of the physiologic and pharmacologic facts underlying the action of alcohol upon the body. We all know that when alcoholic beverages are swallowed, alcohol is rapidly absorbed from the gastro-intestinal tract into the blood stream. In most persons this absorption is nearly complete at the end of the first hour. Alcohol is carried by the blood to all parts of the body, where its primary action is that of a depressant of nerve function. In the various organs of the body, particularly in the liver, alcohol is oxidized, or burned, just as the body burns starches or sugar. This destruction of alcohol by oxidation in the body constitutes the chief means of sobering up. On the average, the body burns alcohol at the rate of about ten grams per hour, or the equivalent of two-thirds of an ounce of whiskey per hour.

Since alcohol exerts its primary effect in depressing nerve activity, one would expect that the degree of nerve depression would be more or less proportional to the concentration of alcohol which is being carried to these nerve centers, or, in other words, to the alcohol concentration of the blood. Many independent researches by experimental psychologists, physiologists, and pharmacologists have shown this to be true. Therefore, if we know the concentration of alcohol circulating in a person's body, we have a reliable quantitative index of the extent to which he is "under the influence."

The question will be immediately posed: "How can that be true when we know as a matter of common knowledge that persons vary widely in their susceptibility to alcohol?" The answer is that while there is a wide range of tolerance to alcohol which is swallowed, there is very little variation in response to alcohol which is circulating in the body. The difference is due to variations in the rates of absorption and oxidation of alcohol. The susceptible person probably absorbs his alcohol rapidly and burns it slowly, whereas a more resistant or habituated individual absorbs his alcohol more slowly and burns it more rapidly. In other words, two men may respond

to alcohol quite differently. Given the same dose, the one will become definitely drunk while the other may remain entirely sober. However, if we analyze the blood of the two men, we will find a much higher concentration of alcohol in the man who was susceptible than in his more sober associate. If, now, we give additional liquor to the more resistant man so that the concentration of alcohol in his blood is raised to the same amount as in the blood of the more susceptible individual, then both men will be equally intoxicated. In other words, within a reasonable degree of variation, which I would estimate to be between a plus or minus 10 to 15 per cent, all men are equally intoxicated when they have equal concentrations of alcohol circulating in their bodies.

One need not obtain blood for such an analysis; very satisfactory results may be obtained from an analysis of urine, breath, or saliva, for these also reflect the amount of alcohol which is circulating in the body. The same blood which carries alcohol to nerve tissue to produce intoxication also passes to the kidneys, lungs, and salivary glands, where small but proportional amounts of alcohol are secreted into the urine, breath, or saliva. Thus, if we know the alcohol concentration of these, we have a measure of the concentration of alcohol circulating through the body, and hence an index of the resulting degree of impairment or of alcohol intoxication. Naturally, in taking samples of breath or saliva, one must make certain that no alcohol remains in the mouth as a residue from recent drinking. However, such residual alcohol disappears within 15 to 30 minutes after taking the last drink.

My friends of the legal profession often point with alarm to the degree of variability in humans, which I have estimated at about plus or minus 10 to 15 per cent. It would be very desirable if we could evolve a mathematical formula which would encompass all mankind, but this seems very far in the future. Nevertheless, our courts have a right to demand the best evidence which can be produced in order that justice may be done. And with all allowances for human variability, it seems that there can be little question that chemical tests for intoxication do serve as an extremely important adjunct to physical indications. They not only serve to convict the guilty, but which may be more important, they protect the innocent.

With reference to the operation of a motor vehicle upon the public highways, the recommendations of

the National Safety Council and the American Medical Association seem to provide an admirable answer in the safe interpretation of chemical tests. Their recommendations, as embodied in the statutes of such states as Indiana, New York, Maine and Oregon, classify cases into three categories, as follows:

1. Where there is less than 0.05 per cent alcohol in the blood or equivalent amounts in other body fluids or breath, the subject shall be presumed to be not under the influence of alcohol so far as the operation of a motor vehicle is concerned.

2. Where there is 0.15 per cent or more alcohol in the blood, or equivalent amounts in other body fluids or breath, the subject is presumed to be under the influence of alcohol, as far as the operation of a motor vehicle is concerned.

3. Where there is between 0.05 per cent and 0.15 per cent alcohol in the blood, or equivalent amounts in other body fluids or breath, the results of such tests may be received along with other tests or observations for consideration by the court or jury as bearing upon the question of alcohol influence.

This arrangement adequately safeguards the interests of the person who has been properly temperate in his drinking. Impairment sufficient to adversely influence driving ability is demonstrated quite clearly in the average individual at alcohol concentrations of 0.09 per cent to 0.11 per cent in the blood. Thus, the establishment of 0.15 per cent as the presumption limit gives a considerable degree of grace for individual variation, which protects the most resistant or tolerant driver and also makes allowances for the mild antidotal effect of coffee, caffeine, benzedrine, and similar stimulants which might have been taken.

While these quantities of alcohol seem almost negligible, it should be realized that for the average adult it requires at least two twelve-ounce bottles of beer or two one-ounce glasses of 100-proof whiskey to bring an individual up to the lower blood limit of 0.05 per cent alcohol. To reach the presumption level of 0.15 per cent alcohol in the blood, the average man must consume six to eight bottles of beer or six to eight ounces of whiskey.

It would appear that if we are to employ the best evidence which is available concerning the sobriety or degree of alcohol influence of an individual in court actions, we must, of necessity, employ the chemical tests for intoxication to confirm medical observations of outward signs and indications.

# Legal Problems Regarding Blood Grouping Tests in Paternity Cases and Scientific Tests for Alcoholic Intoxication

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The need for scientific tests for determining paternity is well illustrated by an incident that occurred down south a few years ago. A young unmarried mother was being investigated by a social worker, who tried to find out who the father of the child was. If she found the father, the county would be relieved of financial responsibility for caring for the young one. Her efforts were futile. She called upon the county judge and asked him if he wouldn't help try to find out who the father of that child was. The old judge said, "All right, have the young lady brought in here and we'll see if I can help you."

As the unmarried mother approached the bench, the judge said, "Young lady, who is the father of your child?"

She looked up at him and said, "Judge, I can't tell you."

He said, "Come now, my child, who is the father of your baby?" She persisted in saying, "I can't tell you, judge." The judge by that time was losing his patience, and the young lady looked up at him and said, "Judge, have you-all ever been around a sawmill? Have you ever seen that buzzsaw running around?"

"Yes."

"Well, Judge, if you put your finger on the buzzsaw and get it nicked, do you reckon you could tell what tooth bit you?" That is the problem that the courts are up against repeatedly in these paternity cases.

All that the courts usually require of a test of a scientific nature before accepting its results as competent legal evidence is that the test has a reasonable measure of precision in its indications and is an accepted one in the particular profession to which it belongs. Blood grouping tests meet this requirement, and with a far greater measure of precision than is found in certain other types of acceptable scientific evidence. The test results are admissible, and have been so held in a number of appellate court decisions. In Maine, Maryland, New Jersey, New York, Ohio, South Dakota, and Wisconsin the test results are declared admissible by statute. Apart from the fundamental issue of mere admissibility, however, blood grouping tests give rise to several interesting and important legal problems. In the first place, what weight should be given to the test results by the courts? The

scientists say the results are exact and absolute, or nearly so. If that be true, should the courts consider the results as conclusive evidence of the facts in litigation? Then there is the problem of whether evidence should be admissible as regards the possibility of paternity or restricted to cases where the results prove the impossibility of paternity. In other words, in addition to permitting an accused father to prove that his blood type is incompatible with that of the child and thereby being eliminated as the potential father, should an accusing mother be permitted to prove that the blood type of the alleged father is such that he could be the child's parent? Another problem: do the courts have the inherent power in a civil suit to compel one of the litigants or the child to submit to a blood grouping test?

Several years ago in California a 70-year-old man was named as defendant in a bastardy proceeding. The accusing mother was considerably younger, had been married twice, was the mother of several children, and was separated from her second husband at the time of the conception and birth of her youngest child, whose parentage was in controversy. The plaintiff testified that the defendant had been paying her rent and furnishing food and clothing for her and her family. She testified that he visited her twice a week for three years, and had frequent relations with her. A number of witnesses testified they saw defendant visit plaintiff's home on many occasions. A nurse who cared for the plaintiff at the time of the child's birth testified that the defendant paid her for her services and on several occasions brought groceries and clothing for the baby. The defendant denied ever visiting plaintiff's home, or that he had ever been intimate with her. Both the defendant and his wife testified he was impotent.

Upon the defendant's petition, a physician selected by the court made blood grouping tests upon the mother, the child, and the defendant, and testified that the two adults were of group O, whereas the child was group B, which grouping in the child could have been present only if at least one of his parents was of group B. In other words, the 70-year-old man could not have been the father, so the physician testified. The physician's testimony was not refuted by any expert testimony on the other side.

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The trial resulted in a finding by the court in favor of the plaintiff. The 70-year-old defendant was legally declared to be the father. And the trial court's finding and judgment was affirmed by the Supreme Court of California.

The Supreme Court said: "Whatever claims the medical profession may make for the test . . . no evidence is by law made conclusive or unanswerable, unless so declared by the code. . . . The law makes no distinction between expert testimony and evidence of other character. . . . When there is a conflict between scientific testimony and testimony as to facts, the jury or trial court must determine the relative weight of the evidence."

The California District Court of Appeal had taken a different view when it reversed the trial court in the following words: "A finding of fact based solely upon the testimony of a witness contrary to a scientific fact will be set aside by this court as not supported by substantial evidence." This view is naturally the one sought and hoped for by the medical men and scientists; but the various courts which have considered the problem have adhered to that expressed by the California Supreme Court, that when there is a conflict between scientific testimony and testimony of any other sort, the law itself will grant no preference; and the relative weight of the evidence is to be determined by the jury or by the trial judge in a nonjury case.

There is much that can be said for each point of view. Many members of the legal profession feel that even conceding the exactness of the science, there is no positive assurance that the witness has correctly applied the scientific principles, or that the scientist may not have had his price for a perjured conclusion. Permitting such conclusive effect to be given to the defendant's expert testimony would make it imperative for the plaintiff to also seek expert assistance, which luxury she may be unable to afford. To accept the view that the test results are conclusive means a willingness to forego the right to a jury trial. For all practical purposes it means that the scientific witness becomes also the judge and jury.

On the other hand, there is respectable opinion among some lawyers that whatever potential evils may be present, the court can safeguard itself against them. There is the protection afforded by the court's power to critically examine the qualifications of the tendered expert, and refuse to permit him to testify if his training, experience, and standing in the profession is not such as warrant the risk of his opinion. The courts of New York City have worked out an excellent plan to insure reliable and trustworthy ex-

pert testimony in bastardy cases. Under the New York statute the court is empowered to appoint "a duly-qualified physician" to conduct the tests, and in the exercise of that right the New York City courts appoint only those physicians whose names appear on a list of qualified experts supplied the courts by the New York Academy of Medicine. A rather foolproof system is also used in New York in such cases to guard against the possibility of a suitable substitute for one of the parties, or of the child being submitted for the taking of the blood specimen. The New York system has worked extremely well.

Under a system such as that employed in New York City, or under any comparable procedure that will insure honest and competent experts, perhaps the courts could safely decree that conclusive weight is to be given to the scientific testimony. Under any other system which does not guarantee such honesty and competency of the expert witness, perhaps it would be too risky to follow any other course than that laid out by the Supreme Courts of California and Ohio, to the effect that the weight to be given blood grouping expert testimony is a matter within the discretion of the jury or the trial judge, in nonjury cases.

Now for the second problem: As Dr. Davidsohn told you, the test can only establish or prove non-paternity, that the alleged father could not be the child's parent. As yet, the scientist cannot say that a particular individual is the child's father. Therefore, since the tests can only prove exclusion (that the accused is not the father), are results which indicate mere possibility of paternity (that the accused may be the father) of sufficient value to be admitted in evidence? Dr. Davidsohn says "No," and upon this point the scientist and the courts agree. While logically relevant as concomitant evidence, it seems that the possibility of prejudicial inference against the defendant is too great in return for the remote evidence of capacity. The courts have so held, and the statutes upon the subject also restrict the evidence to the establishment of the fact that the defendant could not possibly be the child's father.

Do the courts have the inherent power to compel one of the litigants to submit to a blood grouping test? Not only does common sense and good reason produce a yes answer, but there is also no valid reason in point of law to indicate a different answer. As a matter of fact there is considerable legal authority to support the view that such compulsion is permissible. There is first of all the ancient writ *de ventre inspiciendo*, whereby the body of a woman feigning pregnancy could be examined, a writ giving an heir presumptive the right to have a widow ex-



amined in order to ward off any attempt of a false claim against the estate. Then, too, it has always been considered proper in a divorce case based upon an impotency charge, to compel the party-opponent to submit to an inspection. The United States Court of Appeals for the District of Columbia in a 1940 case held that under Rule 35 of the Federal Rules of Civil Procedure, a mother and her child could be compelled to submit to blood grouping tests where the child's paternity was in question. Obviously, of course, there being no constitutional difficulty involved, the legislature can provide for compulsory testing, and the statutes upon the subject make such provision.

#### TESTS FOR ALCOHOLIC INTOXICATION

Scientific tests for alcoholic intoxication have a reasonable measure of precision in their indications. The tests results are clearly admissible in evidence, and the cases so hold. The tests are specifically legalized by statutes in Indiana, Maine, New York, and Oregon. But just as with blood grouping tests, there are certain legal problems not so easily solved as the mere issue of admissibility. First and foremost (and the only one of which time will permit any discussion) is that problem regarding the constitutionality of compulsory tests.

Can an arrested motorist who is accused or suspected of driving while intoxicated be compelled to submit to a scientific test for alcoholic intoxication? The answer should be yes, for two reasons.

A study of the historical development of the privilege against self-incrimination will readily disclose that the primary purpose of the privilege was to put an end to the early practice of employing legal process to extract from a person's lips an admission of his guilt. This fact of its origin and purpose is irrefutable. It was not designed to afford protection from compulsory physical examinations conducted for the purpose of establishing identity or for ascertaining certain facts of a physical nature indicative of the guilt or innocence of the accused person. And there are many appellate court decisions to the effect that an accused person may be compelled to submit to an examination of his body for scars, marks, and wounds, and to the taking of his fingerprints or his photograph; to place his foot in a print at the scene of a crime for comparison purposes; to change his wearing apparel or enact a crime for purposes of identification. One court, in a case which involved a problem similar to that regarding compulsory examinations for intoxication, held that an accused person's privilege against self-incrimination was not violated by his being forced to discharge from his mouth some morphine which he

had concealed there when arrested for its unlawful possession.

Upon analogy of these various types of compulsory evidence, the taking of a specimen of breath, blood, or urine cannot be considered as violative of the privilege against self-incrimination.

Of the few cases in which appeals have been taken where alcoholic intoxication tests were made and the issue of self-incrimination was raised, the appellate courts in most instances side-stepped the problem by a finding from the record that the defendant did not object to the tests, and that was considered the equivalent of consent. There is, however, a decision of the Texas Court of Criminal Appeals holding that a compulsory test violates the constitutional privilege against self-incrimination. On the other hand, an Ohio Appellate Court case permitted a conviction to stand where the prosecutor commented upon the refusal of the defendant to submit to a blood test for alcoholic intoxication, the court holding that the constitutional privilege related only to compulsory utterances. And there is a very recent decision of the Oregon Supreme Court holding that the tests did not constitute a violation of the privilege against self-incrimination, although the facts of the case involved a situation where the blood sample was taken from the defendant while he was unconscious, and not over his specific objection.

To my knowledge there are no Illinois cases upon this subject. We do have, however, a regrettable obstacle in the form of an opinion of the attorney general, which caused the present governor to veto a bill very similar to the statutes in Indiana, Maine, New York, and Oregon. The attorney general found the bill objectionable not because of any constitutional difficulty, but on the ground that it did not prescribe a particular type of test of proved accuracy. The assistant attorney general who prepared that opinion apparently was unaware of the general acceptance of the test among scientists, and of the legislation in these other states and the legal decisions in other jurisdictions specifically in point. At least no reference is made to them in the opinion, which drew an analogy between such chemical tests and lie-detector evidence. The one, of course, far surpasses the other in accuracy, and no competent expert in the field of lie detection recommends the judicial acceptance of lie-detector evidence at the present time. But there is widespread approval of the court use of chemical tests for intoxication. I trust that upon some future occasion the matter will be given more serious consideration than is evident from the attorney general's opinion now on the books.



Even if it be assumed that a compulsory test violates the privilege against self-incrimination, which I certainly do not recommend, there is another theory for supporting the legality of compulsory tests for alcoholic intoxication. A state legislature can by an enactment remove all doubt as to the legality of such tests and overcome the alleged existence of the privilege. The theory is simple. It is an undisputed fact that it is within the police power of a state to regulate the use of the highways for the protection of the public. The use of the highways is a privilege, and not a right. The legislature can, if it so desires, exclude automobiles from its highways and streets altogether. If the privilege can be denied, the state can grant the privilege conditionally. If such a condition be that any motorist using the state's highways and streets who is accused or suspected of being intoxicated must submit to a scientific test for alcoholic intoxication, then the motorist can be deemed to have waived the constitutional privilege he may otherwise be assumed to have. In other words, the power to prohibit includes the power to impose conditions of use. When the motorist uses the highways, he assumes the conditions attached to the use. Even if the privilege is assumed to exist, it can be considered waived, and there is no doubt that such a privilege is subject to waiver.

Although as yet there are no decisions which have considered the problem in this manner as regards tests

for alcoholic intoxication, there is a group of cases which have paved the way in that direction. For instance, in a New York case, in which the defendant was accused of violating a statute making it a felony for anyone to knowingly leave the scene of an accident without stopping and disclosing his name, address, and license number, the defendant attacked the statute on the ground that it called for a violating of his privilege against self-incrimination. The New York Court of Appeals sustained the conviction on the theory that by using the highways with that statutory condition attached to such use, the defendant motorist waived any possible privilege against self-incrimination. The court made the statement that it was no "violation of public policy or the principles of personal liberty to enact that, as a condition of operating such a machine one must waive his constitutional privilege." Similar statutes have been upheld in California and New Hampshire. We have such a statute in Illinois. A statute relating to tests for alcoholic intoxication should be viewed in the same light. A court should have no difficulty in holding that a statute of this nature attaches a condition to the motorist's privilege in using the highways, and having done so he waives his alleged right to immunity to the compulsory taking of samples of his urine, breath, or blood for purposes of an intoxication test.

## Discussion

QUESTION: Doctor, in Evanston I understand it is customary to give a test where they have them breathe into a container. There was a case tried in our lower court in which a chemist came in from the South Side of Chicago, and he testified that where the technician who makes the test is a police officer, although he has been trained over at Northwestern University, he wouldn't be sufficiently skilled to take into consideration all the control factors that should be observed, and therefore, the testimony would be worthless. I want to ask Dr. Muehlberger if there are practical difficulties in training the police department to give these intoxication tests, or are the controls that the policeman would have to employ in order to safeguard the prisoner, simple.

DR. MUEHLBERGER: Whether or not a police officer could be easily trained as an expert analyst presents somewhat of a problem. I have known of police officers who take training and who become quite competent in the use of the technic. On the other hand, I wouldn't want to say offhand that any person who has handled the apparatus a short time would be competent to make the analysis, and I think that is a matter for the court to take into consideration. I do know of instances where police officers with a reasonable amount of training and a month or two of experience, have proved to be quite adept and quite accurate

in making the tests, and also in observing the precautions which are essential to getting an accurate analysis. Such precautions are chiefly those of cleanliness and of precision in measuring chemicals.

QUESTION: I would like to ask one question which was not brought up, and that is the element of time lag between the accident and the time of taking the test. Witness an individual on a highway, an accident, a time lag before the highway police arrive, more time lag until the man arrives at the police station, multiple argumentation; finally, two or three hours later, the test. What is the rate of drop, Dr. Muehlberger, in percentage by computation, on an average adult, of average stature, per hour, per percent? Can you estimate that?

DR. MUEHLBERGER: Under the circumstances which you state, I would say that the estimation would be just that; it would be an estimation. As I pointed out, persons don't all oxidize alcohol at the same rate, and all that the test will do is determine how intoxicated the person was at the time the test was made. How intoxicated he was at some previous time becomes more and more problematical as the length of time elapsing between the accident and the test becomes greater and greater.

QUESTION: I would like to ask a question of Professor Inbau, if I may. You have mentioned the fact that in divorce

cases where impotency is a charge, they have a right to make a party take a test. You are not speaking of Illinois, are you?

MR. INBAU: I didn't make any specific reference to Illinois. That is a power the courts have had from away back.

QUESTION: Do you know of any Illinois case?

MR. INBAU: No, I don't.

MEMBER: You know what the tests are, don't you?

MR. INBAU: Tests for what?

QUESTION: The tests for impotency.

MR. INBAU: I am afraid I will have to refer that to one of these medical men. I don't know. I will say this: Even here in Illinois, in the absence of any statute in point, there is some merit to the contention that under the present set-up, with the Practice Act before us, and whatnot, that a litigant in a personal injury case might be compelled by the court to submit to physical examination. I am sure some lawyers may object to that, but it is not for us here to elaborate on the idea. You will find, again, a rather elaborate comment on it in the Illinois Law Review bearing specifically on that. If you concede the court has the right in civil cases to compel the litigant to submit to an examination in a personal injury case, you are just a short step removed from compelling his submission to a taking of the sample of blood for blood-grouping tests.

QUESTION: I would like to ask Dr. Davidsohn a question in connection with the case mentioned by him where the grouping test was shown as being untrustworthy once in 25,000 cases tested. What thought is given to the fact that there may be freaks of nature discovered, or something in the "believe-it-or-not" field? May it not be the case, as was proved by that one in 25,000 that a case may present itself the result of which may be different from those generally accepted as scientifically true?

DR. DAVIDSOHN: The case that was reported in 1932 was one, as I said, where the mother was found to be of group AB and her child of group O. This is an exception to the second law of inheritance. If it were the case of a father and a child, we would not attach too much importance to it, because one could suspect illegitimacy. We cannot do it in the case of a mother and her child. In this case, then, it was necessary to bring forward some explanation for it, because it is definitely against one of the rules of inheritance. Further information revealed that the child was a deaf-mute, and had a number of physical abnormalities. Thus though there was an exception observed to the second law of inheritance in one out of 25,000 cases tested, there is no known exception involving a normal child. It was suggested by an authority on the subject that there was some kind of genetic abnormality in the case. But even assuming that this was an exception, this would give us an error of one in 25,000. If you have any scientific evidence that can match the accuracy of an error of one in 25,000, and are not willing to accept it, I think you are going a little bit too far.

In the case of all other laws there is evidence going into the hundreds of thousands, and no writer on the subject will deny that theoretically there is a possibility of an exception but it is very unlikely, only one chance in many hundreds of thousands.

QUESTION: Are there any statistics as to the fatal accidents attributable to alcoholism in any degree, or in varying degrees?

DR. MUEHLBERGER: I can't cite you the exact figures. I know the coroner at Cleveland, Ohio, has compiled quite a bit of information on that point. I think his data point to 30 per cent of the fatal accidents on the highways, indicating that where a driver or pedestrian was involved, one of the two or both was under the influence of alcohol. That is a very high figure. Other findings go down to as low as 10 or 15 per cent; and of course, when it comes to determining what percentage are under the influence of alcohol, we have to take into consideration how far one is willing to go in saying when a person is under the influence of alcohol. Are you going to put the figure as low as 0.05 per cent, or some higher figure? The National Safety Council, in compiling figures, I think have given those two extremes, between 15 per cent and 30 per cent of the fatal injury accidents on the highway, involving some person under the influence of alcohol.

MEMBER: A friend of mine quoted some Metropolitan Life figures showing the life expectancy of people in the United States 50 years ago was 42 years, as against present day living of 62 years. The safety of the highway is a problem that seems to me as a lawyer to be one of great importance, as far as the life expectancy of each and every one of us is concerned.

DR. MUEHLBERGER: May I inquire as to whether or not he was holding forth the idea that our increased life expectancy was because of the automobile, or due to some other factor?

MEMBER: He was discussing the challenge of our increasing leisure, due to technocracy and technical advances, and he cited that in India today a person born there has an expectancy of about 27 years. Of course these are all actuarial figures, yet in a country like the United States, where we hastily drive across the country, drunk or sober, we have an expectancy of 62 years.

QUESTION: I would like to address a question to Professor Inbau, and ask him if in the laws permitting intoxication tests there is any method whereby the accused later could secure his own check or own findings. I have in mind the practical situation at the average police station, at probably two in the morning. I am wondering, as long as this is rather perishable evidence, how the accused is protected from what I consider a high probability of fraud being perpetrated.

MR. INBAU: I think you have a perfectly valid objection there to any proposal that these results be taken as conclusive, such as we mentioned is a very plausible thing to try to do with regard to blood-grouping tests. But the practice varies on that. There is, I believe, in some communities, a practice of preserving a specimen for subsequent testing, but it isn't specifically provided in the statutes that there be any specimen preserved. It is not my recollection that the statutes require the preserving of a specimen, so that the defendant later can have the benefit of some expert making a test and checking the results made by the police expert.

QUESTION: Should it not be so provided when we get around to asking for such a law?

MR. INBAU: Dr. Muehlberger might mention to you some of the practical difficulties there with regard to preserving a specimen: how long can a specimen be preserved, and how should it be preserved to afford the defendant that opportunity? For that reason I don't think you could validly argue that the results of a test for alcoholic intoxi-

cation could be taken as conclusive. There is that privilege denied the defendant, which is not denied the plaintiff in blood-grouping tests. In other words, that test can be made at any time, at the time of trial or shortly before. You are quite right in voicing that as one defect in this method. Dr. Muehlberger can elaborate on that.

DR. MUEHLBERGER: I believe the gentleman is correct in saying that the law does not provide for the taking of duplicate specimens so that the defendant may have his own expert analyze the specimen. However, that is one of the defects in the use of the breath test for determining alcohol. It is simply impossible to take a balloon full of air and keep it without having the alcohol absorb into the rubber and have the test be rendered worthless. That is the chief value of the taking of specimens of such materials as blood or urine, or even saliva. One can take a specimen, divide it into two parts, place one in one container and seal it, and place one in the other and seal it, and retain one in a refrigerator until such time as the defense makes a call for it. If no call is made in a matter of a couple of weeks, even in a refrigerator specimens will deteriorate; but specimens taken in duplicate do provide what I think is a fair opportunity for the opposing side to check the accuracy of the analysis.

Of course in any instance of taking a specimen, one has a right to go into the way in which the specimen was taken, the kind of container into which it was placed, the degree of precaution that was taken to see that the container was clean and dry when the specimen was put in, and such matters as how the syringe was sterilized, whether it was sterilized in alcohol—which has happened in taking an alcohol test, thus throwing a certain amount of doubt into the validity of the test itself. Those things should be brought out in the interrogation. I think they are very proper and very necessary in safeguarding the rights of the individual who is being tested.

QUESTION: The question of the exclusion of paternity suggests that the evidence is similar to other alibis. I wonder if it doesn't carry that type of weight.

MR. INBAU: I don't know that I fully understand your question.

QUESTION: It seems to me proof of exclusion is like an alibi. I wondered if the tests that exclude paternity are in the nature of alibis.

MR. INBAU: I would say it was a pretty good alibi.

QUESTION: Is it treated like other alibis?

MR. INBAU: Do you mean that being a very strong alibi, nevertheless, you have no right to attach conclusive weight to it?

QUESTION: That is what I should think, or that it should not be thrown out any more than any other valid alibi?

MR. INBAU: Even the courts that do not take it as conclusive still use the evidence for what it is worth, along with the other evidence in the case. The only real difference of thought on the subject is that when the scientist comes in and testifies that it is impossible for the defendant to have been the father, are we going to then say that that offsets anything the plaintiff may have offered in the way of evidence? The courts thus far are refusing to do that. The main objection to accepting the results as conclusive, it seems to me, is that you have no assurance that the expert is honest and competent, and as long as you don't have that assurance, I don't believe the results ought to be taken as conclusive. But under a system such as you have in New

York, where the only experts used are those approved by the New York Academy of Medicine, it seems to me that in that instance, we ought to go the length of taking it as conclusive of the matter in issue.

The question was raised whether or not there couldn't be a fraud perpetrated, a frame-up. Never lose sight of the fact that if the police set out to frame somebody there are a lot of other ways of doing it, a lot simpler ways of doing it. From my work with policemen over a period of years, I know of some instances where there were attempts at frame-up. All they need do is put a key in somebody's pocket that fits the door of the place they want to prove he went into, and that is going to be just as good a frame-up as if you falsified evidence of a scientific nature. I am talking about a criminal case now. Naturally there may be frauds perpetrated with scientific evidence, but you are not going to have any more perpetrated because it is scientific.

QUESTION: I was going to comment on Professor Inbau's statement about the lack of consent to the examination. I doubt if any law would prevent an individual from the use of the highways. I think I remember the article you referred to, and if I am not mistaken, instead of limiting the use of the highway, the article said that the use of the highway may be licensed, and a license might be withheld from an individual who failed to comply with the law and submit to the examination. I may be wrong on that. An analogy may be the law that we have here providing for substituted service in suits against foreign drivers of automobiles causing injury in Illinois. The theory upon which we are able to get service upon a person from another state who causes accidents in Illinois, having service upon the secretary of state, is that the person has no right on our highway, being a foreigner, and that, by coming to Illinois and using our highways, he thereby subjects himself to the law which provides for substituted service. I doubt if a law of that kind could be applied to a resident of Illinois.

Coming to the matter, as I say, of personal privilege, which we recognize more as applied to the matter of unwarranted searches under the criminal law, the rights of personal privilege are being overrun every day. It is a very serious question how far we can tear down the old concept of personal privilege. We have our home, which is our castle. There are certain things that a person is permitted to do that are personal to him, which ought not to be taken from him without excuse, to say the least. I have in mind a case that I read some time ago. A lady had a lawsuit pending, a personal injury case, and she was in a hotel with her sister, or some other person, and while they were in the room they discussed the facts of her case. Some industrious investigator secreted himself in the next room, and by means of some hearing device, was able to hear the conversation that occurred in her own private bedroom. The case went on for trial, and I think that it was an appellate court case. She was confronted with the statements of what the investigator had heard when the investigator took the stand to impeach her. The court held that that was a violation of her personal privilege; that the testimony was obtained against her will, without her consent, was in violation of her rights, and that it was an error to permit the testimony to be received in court.

Now, when a person is intoxicated and you take from him a sample of his blood without his consent—it may not

be against his consent, but it is without his consent—it would seem to me that that is a violation of a personal privilege. On the other hand, I am somewhat horrified to hear of the large percentage of accidents which is now supposed to result from intoxication. If we are confronted with a situation where approximately 30 per cent of our highway accidents result from intoxication, it is probably time for us to give up something of our personal privilege, and something certainly ought to be done about it. Until we get to the point where we can have confidence in those who make the tests, and know that they are being made scientifically and honestly, it seems to me that we ought to pause before we adopt any such legislation.

MR. INBAU: The article in the Illinois Law Review, developing this notion that I expressed, did deal with it on the basis I described, and with a view not of depriving somebody of a license. It went into the problem of whether or not the use of the highways is a privilege or a right, and the conclusion arrived at was that it was a privilege and not a right, that a condition could attach to the privilege, and that a reasonable condition would be the requirement that a motorist must, if suspected or accused of alcoholic intoxication, submit to the taking of a specimen of blood.

On the second point, regarding the foreign motorists, both of the cases I mentioned dealt with a resident motorist. The *Rosenheimer* case in New York held that the use of the highways was a privilege, even to a resident, and the case did involve a resident, not somebody just passing through the state. The language used in the opinion was quite broad, and it dealt with the general proposition. Then there is the Missouri case of *ex parte Kneedler*, which went on the theory that it was a proper exercise of police power. It took a little different tack from the matter of waiver, but arrived at the same result. There is a case, I believe it is a Maine or Massachusetts case, in which the city fathers decided they didn't want any automobiles at all on certain streets and in certain sections of the city. The validity of that was tested, and the court held that no one had an inalienable right to use the highways; it was a privilege, and the state could deny the privilege altogether. The court held that the privilege could be taken away altogether. It went very far in that direction. I think the way is paved for that possible solution to it, but as I said at first, I don't think you can validly support the objection that the tests themselves do violate the privilege. I don't think they violate the privilege in the first instance. I don't think you have to get to the second way out, the subterfuge, and that is what it amounts to. I don't see how historically or otherwise you can say it is a violation of the privilege. Granted there should be some limitation on how far law enforcement officers and investigators should be permitted to go. I am all for that. There should be limitations, but let us make them reasonable limitations. As regards the case you described of somebody listening in on a private conversation in a bedroom, maybe that privilege should not be taken away from us; but on the other hand, doesn't the innocent man accused of being a father have some privilege worth looking into, as to whether or not he shouldn't have the privilege of proving his nonpaternity? It seems to me there you are dealing with something different, and here in Illinois I am not too hopeful, as I see the cases, as to what the Illinois courts will do on most of these problems. I have in mind particularly what our

courts have done with regard to search and seizure. The Constitution prohibits unreasonable search and seizure. The Illinois Supreme Court has progressively placed restrictions on law enforcement officers in their investigations, until now we are at this point, and I think it is a ridiculous one. Some of you may recall the pheasant case, where a game warden was tipped off that a couple of men on a train had been out shooting hen pheasants, which is against the game laws. He was advised that these two men were getting on the train, and the game warden went on the train, and saw a couple of hunters sitting down, one with some pheasant feathers sticking out of his pocket. They met the description of the hunters shooting hen pheasants, he made an arrest and pulled out the pheasants, and they were hen pheasants. The defendant was prosecuted for shooting and possessing hen pheasants. He appealed the case to the Supreme Court, and the Supreme Court held this, that this was an unreasonable search and seizure, because when the game warden saw the pheasant feathers, he didn't know whether they were hen pheasants or cock pheasants.

It seems to me that is protecting our privileges to an unreasonable extent. We have to bear in mind the historical origin and the basis for the rules. There is an example where I believe our courts, certainly in this state, have been overlooking the other side of the picture. There is the interest of the public to be served, and I think we are straining a lot of the constitutional privileges. Let us preserve them, but within reasonable bounds. I don't think the pheasant case speaks well for what we might expect in some of the other matters we have been talking about.

QUESTION: In the interest of protecting the public, I would like to ask Professor Inbau what the thinking of the courts might be in questions of this nature: a pedestrian is struck by an automobile, the pedestrian is killed. He is taken to the hospital near by, or to the county morgue. Blood from the dead person was submitted for alcoholic examination. The case comes to court. First, will the blood level indicating intoxication of the blood taken from the dead person be allowed in evidence, and if so, what protection has the public in reference to the driver of the automobile where, by your interpretation of self-incrimination, such examinations are not allowed?

MR. INBAU: You are talking now about a pedestrian, he is not being prosecuted for any crime, himself. He is not a defendant; is that your case?

QUESTION: No, the submission of the evidence that the pedestrian was intoxicated, because blood was withdrawn for such an examination, whereas the man who drove the automobile is protected because of your interpretation of self-incrimination.

MR. INBAU: In other words, if you will permit the evidence of the pedestrian as proof that the defendant was not responsible for the accident, it certainly ought to work the other way, and the defendant ought to be required to give a specimen, if one is so desired, for determining whether he was intoxicated.

QUESTION: At the time of the accident.

MR. INBAU: At the time of the accident. Your point is that it ought to be equalized, and you have two rights to deal with, the right of the injured party or the public, as against the rights of the defendant. That is my point. It seems to me we should not lose sight of the fact that you really have two privileges that should be kept in mind; the

privilege of the defendant, and the privilege of the public. Certainly I don't know of anyone that would propose abolishing the constitutional privilege against unreasonable searches and seizures. It serves a very valid service. Neither you nor I want some officer kicking our door in at night and tearing the place apart looking for evidence, but certainly if I am out shooting pheasants and somebody tips off an officer that I am shooting hen pheasants and he sees a pheasant feather sticking out of my pocket, I think he ought to have a right to pull those feathers out and see if they are hen pheasants or cock pheasants. I don't think the constitutional privilege was intended to go that far.

QUESTION: I suppose when they shine bright lights in a person's face, shine bright lights in his eyes, and make him stay up all night, that may hurt the person more than taking a little blood or drawing a little urine. Couldn't you set some standard by the harm done to the person, rather than other interests? It is actually harder on the person, where they make him sit up all night, or something like that.

MR. INBAU: There is no question that by not availing ourselves of the scientific methods of proof we do, in effect, offer encouragement; at least we tolerate, anyway, the use of the cruder methods which are not so accurate in their results, and they may well get an innocent man into trouble. Now, as Dr. Muehlberger mentioned to you, these tests for alcoholic intoxication can serve well the innocent man who is accused. It doesn't mean that every time you take a sample of blood and analyze it, somebody is going to jail. Dr. Muehlberger could have told you of instances where people in a diabetic coma, or something like that, may have all the symptoms of an intoxicated individual, but you take a specimen of blood and analyze it, and you will prove that that person was absolutely sober. There is an innocent man who is not getting in trouble. But if you left it up to the police officer to describe the looks of the man found behind the wheel of the car climbing a telephone pole, the defendant might well be convicted of driving while intoxicated, and what you say is perfectly true. Certainly, as between the two alternatives, or the two situations, it is far more desirable to subject somebody to the giving of a sample of blood than it is to permit the police, or at least not to do anything to discourage them from using brutality in getting confessions from accused persons.

QUESTION: I have in mind a man whom you say absorbs liquor in the system slowly. If that man takes a number of drinks rather rapidly, gets in his automobile, has an accident five minutes thereafter, at the time he appears perfectly sober, and fifteen minutes to a half hour later it appears that he has liquor on his breath and is then given a sobriety test, the effect of which shows at that time he is conclusively intoxicated. Is there any way of determining that he was sober at the time of the accident? I have this in mind. Presumably he is further faced with a lawsuit as a result of the accident, and he has five witnesses to say he appeared to be sober at the time. We do have sobriety tests, which take precedence in the jury's mind. Is there any way you can determine whether he is sober at the time?

DR. MUEHLBERGER: No, the test only indicates his condition at the time the test was taken. What his condition was prior to that depends on other evidence. In proper investigation one doesn't rely only on chemical tests. He makes other inquiries; and most police departments have a regular form to fill out, which includes such questions as: "Have you been drinking?" and "What have you been drinking?" and "When were you drinking?" and, "When did you take your last drink?" The answer to those questions may be very important in interpreting the chemical test which is made later on. If a man really did his only drinking just before the accident and the test was not made for perhaps another hour, he might very well be under the influence of alcohol at the time the test was made, although entirely sober at the time of the accident. It does take time for alcohol to be absorbed, so that the interrogation of the subject may be very important in showing what his condition was at the time of the accident. I am not suggesting that the chemical test alone is the only answer. It serves as a very useful adjunct in interpreting the other evidence such as a man's statements, and observations of others as to his condition.

CHAIRMAN GEILING: I should like to conclude this meeting and again I wish to express on behalf of the sponsors, our best thanks to those who came here and lent their support. To the speakers, I am sure I am voicing the opinions of the audience by saying that they have given us a very enlightened and scholarly presentation. May I, for myself, say that I have hope that there will be a continuation of many more meetings of a similar kind. Chicago has led, and I hope other cities will follow that lead.

### Coming In April

Rocky Mountain Spotted Fever

*George T. Harrell, Jerry K. Aikawa and Weston M. Kelsey*

Influence of Complications on the Treatment of Peptic Ulcer

*Lowell B. Snorf*

Amino Acids in Nephrosis

*Douglas MacFayden*

Short-Term Psychotherapy

*Harriot Hunter*

Clinicopathologic Conference

*Boston University School of Medicine*

# Lymphogranuloma Venereum\*

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WASHINGTON, D. C.

*For the physician interested in venereal disease or for the one who provides medical attention for members of the colored race, the review of the clinical manifestation of this disease should be of interest.*

## SYNONYMS

This is a disease recorded in medical literature by many names. The accepted nomenclature is lymphogranuloma venereum. Equally descriptive and in some respects less confusing is the term lymphopathia venereum. Other names applied to this disease are: lymphogranuloma inguinale, Nicolas-Favre disease, the sixth venereal disease, chancre lymphogranulomateux, bubon d'emble, pestis minor, climatic bubo, ulcus rodens vulvae, syphilome anorectale, ulcus callosum stenoticans recti, poradenitis, and esthiomene.<sup>1</sup>

## ETIOLOGY

Lymphogranuloma venereum is caused by a filterable virus. Characteristics of this virus are its affinity for lymphatic tissues and its susceptibility to treatment with the sulfonamide drugs. The virus is transmitted by sexual inoculation. Rarely is it acquired otherwise. The incubation period is from 5 to 21 days. No race or class is immune to the disease, but it is found most frequently among people of low sex standards and in warm, moist climates. The usual portal of entry is through the genital mucous membranes. A widespread invasion of the infection is suggested by the constitutional symptoms which accompany the acute phase of the disease.

## SYMPTOMS

The clinical reactions to this infection may be classified as local and systemic and as acute and chronic.

**Acute Local Symptoms.** In the early acute phase of the disease, the primary genital papule or ulcer may

go unnoticed. With spread of the disease accompanied by secondary infection, edema, lymphadenopathy, pain, tenderness and suppuration occur. Tender, elongated, "grooved" inguinal bubos, with swelling above and below the groin fold, usually appear unilaterally, but they may occur bilaterally.<sup>2</sup> The inguinal glands are surrounded by periadenitis which causes distention and purplish discoloration of the skin overlying the glands. If untreated, the inguinal nodes break down at different times and drain through multiple sinuses. If acute edema involves the external urethra, the patient will have difficulty in urination. When the rectum is involved, symptoms of acute proctitis will occur.

**Acute Systemic Symptoms.** Associated with the acute phase of the disease are: fever, chills, headache, vertigo, backache, anorexia, nausea and joint pains.

**Chronic Local Symptoms.** In the chronic phase of lymphogranuloma venereum, local symptoms result from hypertrophy, ulceration, secondary infection, fistulae formation, and distortion of structures in proximity to the vulva and vagina. Symptoms range from ulceration and hypertrophy of the vulvar structures to complete incontinence of urine and feces due to vesicovaginal and rectovaginal fistulae. Chronic, purulent proctitis is a common accompaniment of rectal stricture.

**Chronic Systemic Symptoms.** These consist of debility, anorexia, weight loss, anemia, and hyperglobulinemia.

## PHYSICAL FINDINGS

In the acute phase of the disease, the initial site of inoculation may consist of a small nodule, vesicle, or superficial oval area of ulceration. This initial lesion is seldom seen by the physician. Not infrequently, inguinal adenitis is the primary complaint which brings the patient in for treatment. The degree of local tissue destruction and distortion is in line with the lymphatic drainage from the area of inoculation. Findings are frequently more prominent on one side of the vulva than on the other. A very common area of involvement is the fourchet.

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Presented at the postgraduate courses of the American College of Physicians at Gallinger Municipal Hospital, Washington, D. C., on October 21, 1946.

Lymphatic spread of infection from the fourchet into the rectovaginal septum results in edema, secondary infection, and ulceration with the formation of fistulous or sinus tracts into the perineal body. Acute infection may be followed by a perirectal stricture which is usually about four to six centimeters above the anal orifice. The perianal skin and rectal mucosa frequently become edematous and hypertrophied giving the gross appearance of large hemorrhoidal tags. It is absolutely imperative that any patient showing evidence of external hemorrhoids, particularly large, indurated, polypoid tags of tissue at the rectal orifice, be examined digitally to rule out a stricture. The anorectal type of lymphogranuloma venereum is accompanied by a high incidence of serious sequelae such as rectovaginal fistula, rectal stricture, and soft tissue obstruction to childbirth.

In the acute phase of infection, the labia become brawny, indurated, hypertrophied, with large, everted hair follicles and with areas of linear ulceration in the labial and peri-urethral folds. Hypertrophy of the clitoris is quite common. Severe, secondary infection frequently gives rise to irregular perforations of the labia. There is less destruction of the pigmented layers of the skin than in granuloma inguinale. Peri-urethral infiltration may give rise to destruction and fibrosis of the sphincter muscles with a resulting water-bottle type of bladder and urethra.

While lymphogranuloma venereum rarely extends above the lower third of the vagina, distortion of the cervix and vaginal vault can occur with this disease.

Large, deep, irregular areas of ulceration involving most of the vulva give rise to what is known as the esthiomene type of lymphogranuloma venereum. These large, granular, ulcerated lesions are frequently a precursor of carcinoma.<sup>2-4</sup>

### DIFFERENTIAL DIAGNOSIS

In order to arrive at an intelligent diagnosis in ulcerative, hypertrophic, sinus, bubo and stricture forming lesions of the genitalia and rectum, it is necessary to keep in mind a number of different disease entities. Venereal infections are often multiple. It is not uncommon to find syphilis, postchancroidal disease, gonorrhea, fusospirochetal infections and trichomonas complicating the acute or chronic phase of lymphogranuloma venereum. In a series of patients investigated for genital lesions of the vulva, 50 per cent had general syphilis, but only 23 per cent had genital syphilitic lesions.<sup>5</sup> A positive serologic test does not necessarily mean that the lesion under consideration is always syphilis. In addition tuberculo-

sis, cancer, and granuloma inguinale must be considered. Filiarisias rarely occurs in the United States.

In order to keep before us all diagnostic possibilities, we have prepared a chart which lists the differential tests for ulcerative lesions of the genitalia somewhat in the order of their importance.

#### *Differential Diagnostic Tests*

TEST	DATE AND RESULT
Dark field examination	First rule out open syphilis. <i>T. palladium</i> will not take a gentian violet stain.
Serology	Discover syphilis.
Smear and culture	Culture for gonococci and monilia; <i>H. ducreyi</i> is difficult to culture.
Hanging drop examination	Demonstrated trichomonads and oxyuris.
Ducrey skin test	0.1 c.c. Vaccine intradermally. Read 24 and 48 hrs. Positive = 7 mm induration.
Frei skin test	0.1 c.c. antigen intradermally. Read 48 to 72 hours. Positive = 5 mm nodule.
Tuberculin skin test	0.1 c.c. P.P.D. intradermally. Read 24 and 48 hrs.
Biopsy	Fresh spread for Donovan bodies. Fixed slide for microscopic study. FIND CANCER EARLY.

The present Frei test consists of 0.1 cc. of purified chick embryo propagated antigen injected intracutaneously into the left forearm. An intracutaneous control is placed in the same arm below the antigen. A positive reaction is indicated by a firm papule more

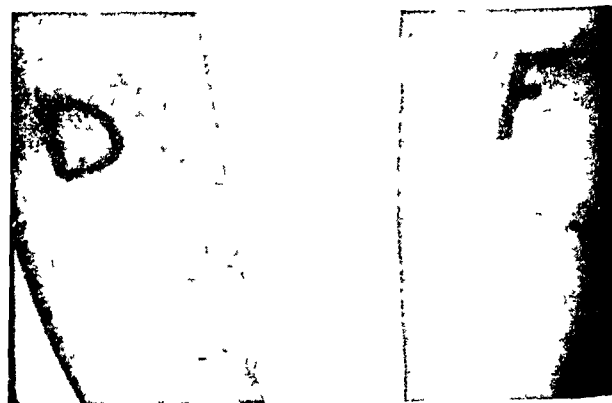


FIG. 1. Positive Frei and Ducrey skin tests.



than 0.5 cm. in diameter appearing 48 to 72 hours after injection. The control reaction should be much smaller. Erythema alone is not indicative of sensitization to the antigen. A definitely positive Frei test means that the patient has or has had lymphgranuloma venereum. There is very little evidence of transmissions of the infection through the placenta to the unborn infant.<sup>5</sup>

### PATHOLOGY

While not specific for lymphgranuloma venereum, the histopathology is rather characteristic and may be of definite value in diagnosis. The lymphatic ves-



FIG. 2. (Left.) Acute lymphgranuloma venereum.

FIG. 3. (Right.) Same patient following sulfonamide treatment.

sels are dilated and numerous. Perivascular collections of plasma cells, lymphocytes and fibroblasts are seen. The muscle fibers appear split and pushed apart by the inflammatory process. Giant cells are present. Cytoplasmic inclusion bodies noted by Gamma, are sometimes seen. In the presence of suppuration, granulation tissue and focal areas of necrosis are evident.

### TREATMENT

In all contagious venereal disease, early accurate diagnosis and isolation or segregation of the patient are of inestimable value in controlling the spread of infection. The infected individual should be rendered completely noncontagious before he or she is returned to society.

Unfortunately there is no known method of producing immunity to any of the so-called venereal diseases. Fairly specific therapy is available for each of the venereal diseases, including lymphgranuloma inguinale.

**Medical Treatment.** In the acute phase of lymphgranuloma venereum, sulfonamide drugs, preferably sulfadiazine, will arrest infection and cause complete healing of all tissues not involved by necrosis or extensive fibrosis.<sup>6</sup> None of the sulfonamides, sulfadiazine, sulfonilic acid, sulfasuxadine or sulfaguandine, will resolve the fibrosis associated with vulvar elephantiasis or perirectal stricture. Sulfaguandine or sulfasuxadine are of value in reducing secondary infection prior to dilatation of strictures or plastic surgery involving the bowel. Sulfonamide-containing water-soluble ointments applied to areas of ulceration



FIG. 4. Anorectal type of lymphgranuloma venereum.



FIG. 5. Chronic lymphgranuloma venereum with vulvar hypertrophy.



FIG. 6. Chronic lymphgranuloma venereum with rectovaginal defect.



reduce secondary surface infection to a minimum.

Intracutaneous, subcutaneous or intravenous injections of increasing doses of Frei antigen have been used with beneficial results.<sup>2, 7-8</sup> This form of treatment requires careful and prolonged observation. The antigen seems to reactivate the infection which will then respond to sulfonamide therapy. Roentgen therapy has no place in the treatment of lymphogranuloma venereum. It may hasten suppuration, but is not curative in any respect.

**Surgical Treatment.** Fluctuant buboes should be aspirated with a large needle, but never incised. Incised buboes form infected sinuses. Buboes should not be resected. Extirpation of the inflamed inguinal glands results in draining sinuses and lymphedema of the vulvar structures.

Large, chronic, fibrotic, distorted vulvar structures should be excised. Vulvectomy should be preceded by local treatment until the bacterial flora and fusospirochetes are reduced to a minimum. Where the clitoris and labia are markedly enlarged, it may be advisable to perform a vulvectomy in two stages, removing the clitoris first, establish healing of the areas of peri-urethral ulceration, and then remove the hypertrophied labia. No operation should be performed in the presence of frank secondary infection.

Strictures of the rectum and urethra present the most serious problem in the treatment of chronic lymphogranuloma venereum. Strictures may be dilated digitally or instrumentally. Great care must be taken not to rupture the stricture; particularly is this true of a rectal stricture above the peritoneal reflection. Diathermy may be of some value in reducing edema associated with the perirectal induration of lymphogranuloma venereum. Mention has already been made of the inadvisability of ever removing hemorrhoids without first performing a rectal examination to confirm the character of hemorrhoidal tags and to rule out the presence of a rectal stricture.

### The Atom Bomb and Cancer

During the last year there have been frequent articles and notes hailing the great value that the atom bomb discovery will be to the study of cancer. Statements have been most frequent and most uncritical in the lay press but even scientific publications have indulged. Dr. Ellice McDonald, Director of the Biochemical Research Foundation, hints in his annual report (*The Journal of the Franklin Institute*, December, 1946) that some physicists, chemists and physicians have gone too far in predicting revolutions in medicine simply because radioactive isotopes are produced from the atomic piles. The atomic pile produces these substances, but they are not new to

Plastic operations to repair defects in the vesicovaginal and rectovaginal septa which result from lymphogranuloma venereum are difficult due to the great amount of scarring of these structures. Colostomy is indicated in patients with absolute stricture of the rectum. Resection of the rectum is usually difficult and unsatisfactory due to persistent infection in the endopelvic fascia and obliteration of normal fascial planes by scar tissue. In addition to difficulty in mobilization of the rectum, the shortened mesosigmoid makes closure of the resected bowel ends unsatisfactory and frequently preservation of the sphincter is impossible.<sup>8</sup>

### BIBLIOGRAPHY

1. Von Haam, E., and R. D'Aunoy: Is lymphogranuloma inguinale a systemic disease? *Am. J. Trop. Med.*, 16: 527-546, 1936.
2. Greenblatt, Robert B.: Management of Chancroid, Granuloma Inguinale and Lymphogranuloma Venereum in General Practice, Supplement No. 19 to Venereal Disease Information, U. S. Government Printing Office, Washington, 1943.
3. Fraser, C. K., H. F. Kane, and John Parks: Stricture forming lesions of the female genitals and rectum, *Am. J. Obst. & Gyn.*, 43:698-703 (April) 1942.
4. Deibert, A. V., and R. B. Greenblatt: Malignancy and lymphogranuloma venereum, *Am. J. Syph. Gonorr. & Ven. Dis.*, 26:330-335, 1942.
5. Wilson, C. Leon, and H. Close Hesseltine: Effect of lymphogranuloma venereum on pregnancy, labor, and the fetus, *Am. J. Obst. & Gyn.*, 43:459-467 (March) 1942.
6. Stein, R. O.: Observations on thirty-five cases of venereal lymphogranuloma treated with sulfanilamide, *Am. J. Syph., Gonorr. & Ven. Dis.*, 24:482-521, 1940.
7. Brandt, R., and R. B. Greenblatt: The therapy of lymphogranuloma venereum, *South. M. J.*, 34:941-949, 1941.
8. Kornblith, B. A.: Lymphogranuloma venereum: treatment of 300 cases, with special reference to the use of Frei antigen intravenously, *Am. J. M. Sc.*, 198: 231-246, 1939.

research. As Dr. McDonald points out these same radioactive materials, particularly radioactive sulphur and phosphorus, have been produced by cyclotrons for the last eight years. In addition, the use of "tracers" merely enables the scientists to determine the course of the radioactive substance in the body and has so far shed little light on the mechanisms of growth which are fundamental in the cancer problem. Of course, such research has offered new evidence and may be instrumental in the future in the solution of the cancer problem, but these methods were being exploited long before the appearance of the bomb.

# Abdominal Auscultation\*

PHILIP THOREK, M.D.

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*The author calls attention to a method of abdominal examination which is rarely used. With the experience necessary to evaluate the findings the procedure described by the author may offer the physician assistance in diagnosis.*

Abdominal auscultation still seems to be the neglected child of physical examination. Although a few clinicians have tried to emphasize its importance as a diagnostic aid, its value is not fully appreciated. The literature on this subject is not voluminous; Stevens, Watkins, Lidsky, Charbonnier, Vaughan, Thorek, and others have used this method and have reported their results. Many decades ago the late J. B. Murphy utilized this procedure and taught it to his students.

To understand intestinal motility and its relation to sound requires a review of gastro-intestinal physiology. The term "peristalsis" will be used as a general one to designate a wave of muscular contraction in any hollow viscus. The means by which intestinal movements are regulated are not fully known, however, it is thought that in the small intestine, the vagi increase the tone and motility, and the sympathetic nerves have the reverse effect. It is believed that normal intestinal motility is controlled by means of local mechanical and chemical stimuli which affect the mucosa. Auerbach's plexus probably conveys impulses which bring about this movement. Intestinal movements which consist of a wave of musculature contraction preceded by a wave of relaxation have been referred to as "the law of the intestine" or "myenteric reflex." In the large intestine, the parasympathetic (sacral autonomic) nerves, activate the entire colon with the exception of the ascending and right half of the transverse colon, and are inhibitory to the internal sphincter ani. Nash states that the sympathetic nerve supply is inhibitory to the entire large bowel as it is to the small intestine, but is motor to the internal sphincter ani, inducing closure of that sphincter.

More than one type of movement is found in the

intestinal tract. Cannon has divided peristaltic movements into:

(A) Diastalsis: this is a downward wave of contraction preceded by a wave of inhibition manifested chiefly by the small intestine. When such a wave hurriedly travels two or three feet it is referred to as a "peristaltic rush."

(B) Catastalsis: this is a downward wave of contraction *not* preceded by a wave of inhibition and is chiefly present in the stomach.

(C) Anastalsis: this is an upward moving contraction not preceded by an inhibitory wave, and has been commonly referred to as reverse or antiperistalsis. It is usually found in the proximal colon but may appear as an abnormal manifestation in any part of the alimentary tract.

There are other movements of the intestinal tract that are not strictly peristaltic in nature; for clinical purposes only three of these are important:

(A) Rhythmic segmentation: this is a localized rhythmical contraction which churns the masses of food and is found in the small intestine.

(B) Pendulum movements: this is a to-and-fro movement mainly produced in the small bowel.

(C) Haustral movements: these are local contractions seen in the colonic haustra, and are analogous to the rhythmic segmentation of the small intestine.

Carey is of the opinion that intestinal movements are due to two closely coiled oblique layers of muscle rather than an inner circular and outer longitudinal layer. Bowel sounds are produced by two factors, namely, (1) the contracting muscles and (2) the onward passage of intestinal contents within the lumen of the gut. With a variety of movements there naturally should be a variety of sounds. To describe sounds in words is difficult, therefore, we must use rather commonplace descriptive terms and convey our auditory perceptions by comparing them with analogous sounds from other sources.

One must become familiar with the normal abdominal sounds which can be heard through the stethoscope. Normal peristaltic sounds may be described as clicks or gurgles which have a tendency to

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be continuous or even overlapping. They are relatively homogeneous and usually more continuous than the heart sounds. Some index as to rate must be established, therefore, when peristaltic sounds are slowed to the respiratory rate they are considered diminished, and when several respirations pass without a single peristaltic sound being heard, they are greatly diminished. Conditions which slow peristalsis also have a tendency to make the sounds quieter; louder sounds usually accompany an increased rate or the presence of a peristaltic rush. Various factors alter the rate and tonal quality. For example, peristalsis may be stimulated and sounds increased by the intake of food, drink, alcohol and other drugs. Depression of sound and tone are usually found with starvation, repeated vomiting and the use of depressant drugs. Air-swallowing may produce both booming or explosive noises which are audible without a stethoscope.

A variety of sounds are heard in both the normal and pathologic abdomen; these can only be recognized by constant practice. We have grouped the pathologic sounds into three categories, namely, diminished, increased and abnormal.

#### DIMINISHED SOUNDS

Complete intestinal paralysis produces a complete peristaltic silence. The abdomen in acute diffuse peritonitis was described by J. B. Murphy as being "silent as the grave." Those conditions which produce the quietest abdomen are: perforated peptic ulcer, acute pancreatitis, gunshot wounds and diffuse appendiceal peritonitis. Any effusion be it pus, blood, bile or urine produces a diminution in the peristaltic sounds; not only the type, but the amount of fluid determines the degree to which intestinal motility is altered. We have coined the phrase, "the wetter they are the quieter they are." Hence, incomplete bowel paralysis results in a quiet but not silent abdomen, as is found in lesser effusions, acute appendicitis preceding perforation, effusions associated with twisted pedicles and in the lesser hemorrhage associated with bleeding corpus hemorrhagicum or corpus luteum. A ruptured graafian follicle diminishes peristalsis only to a mild degree. Neisserian peritonitis, because of its localization deep in the pelvis, usually produces a quiet rather than a silent abdomen. It must be emphasized that no condition in the entire abdomen produces as complete a cessation of intestinal movements in as short a time as does a perforated peptic ulcer. We have become reluctant to diagnose this condition in the presence of intestinal sounds. The exception to this rule is the so-called

forme fruste or pin-point perforation which immediately seals itself. Should this be the case, there is only a small amount of spillage and although peristaltic sounds may have been immediately diminished, they will gradually return to normal.

Following abdominal surgery peristaltic sounds usually disappear, and the postoperative abdomen remains quiet or silent for 48 to 72 hours. When the sounds return, "gas pains" are the chief complaint, and although distressing to the patient, are a good omen to the physician. Should these sounds fail to return within the first few days of an intra-abdominal procedure, one must become suspicious of some intra-peritoneal mischief such as peritonitis, hemorrhage or ileus. It is part of our routine to record the type, rate and intensity of the sounds each day. In this era of early postoperative ambulation we have noticed that intestinal sounds return earlier, even 24 hours following surgery; "gas pains" are diminished, and patients frequently defecate within two days, without the aid of enemas. Apparently bed rest has a tendency to diminish these sounds and aids in the production of intestinal stasis and constipation.

#### INCREASED SOUNDS

Peristaltic sounds are increased in incomplete mechanical obstruction, spinal anesthesia, intra-intestinal hemorrhage and following the use of purgatives. In incomplete intestinal obstruction, the increased sounds are produced by the attempt of the bowel to force the intestinal contents past the obstructed point. If the obstruction is chronic, the bowel musculature becomes hypertrophied and the sounds appear more forceful and booming. When the bowel has exhausted itself and can no longer contract, the musculature becomes atonic and peritonitis results. Although peristaltic sounds are increased in intestinal obstruction, it must be emphasized that this is only noted in the early complete case or if the obstruction remains incomplete. When peritonitis develops, whether it is due to intestinal obstruction or not, the sounds gradually diminish and finally disappear. Following intra-intestinal hemorrhage, as is seen in bleeding ulcers and ruptured esophageal varices, the blood within the intestinal lumen stimulates peristalsis as does food. The stethoscope becomes a valuable aid in differentiating intra-intestinal from intraperitoneal bleeding. In the former, peristalsis is increased, but in the latter it is greatly diminished or absent depending upon the amount of blood in the peritoneal cavity. It is possible to follow the course of an intra-intestinal hemorrhage with the stethoscope and determine whether or not the bleeding is continu-

ing or diminishing by the rate of peristaltic sounds. If the sounds continue at an extremely rapid rate, then the intestinal lumen is being filled with blood, but if the peristaltic rate diminishes or returns to normal the bleeding apparently is subsiding. In spinal anesthesia the sympathetic nerves are believed to be paralyzed; this permits the parasympathetic augmentors to act in an unopposed way. If the abdomen is auscultated following the use of such an anesthetic agent, the sounds will be greatly increased.

Obstructional borborygmi are peristaltic sounds which are pathognomonic of mechanical obstruction; they are not heard in any other condition. These sounds are recognized as metallic tinkles which are usually resonating in character. Normally the stomach and large bowel contain gas which is visible on the x-ray film; this is not true of the small intestine, but in the presence of a small-bowel obstruction, such gas plus fluid is present. When a peristaltic wave moves over such a segment of small bowel, the characteristic tinkle becomes audible. It is difficult to explain why these sounds are not heard in the presence of gas and liquid which are normally present in the stomach or large bowel. These sounds must be differentiated from similar splashing metallic sounds heard in complete ileus which can be produced passively by shaking the patient, or by diaphragmatic movements. Abdominal auscultation, therefore, is of value in differentiating a mechanical from a paralytic ileus, since the latter would have no active sounds and in the former the typical borborygmi are present.

### ABNORMAL SOUNDS

Among other abdominal sounds which might be heard with the stethoscope are: transmitted and respiratory vibrations, liver and splenic friction rubs, the splashing sounds of pneumohydroperitoneum, the bruit of abdominal aneurysms, crepitation from subcutaneous emphysema and according to Charbonnier, the "bruit de collision" of gallstones knocking against each other. It must be admitted that the last mentioned sound seems a little far fetched.

Normally, cardiac and respiratory sounds are not transmitted through the abdomen, but they are heard throughout the distended abdomen. If such distention is associated with diffuse peritonitis or complete obstruction, the cardiac and respiratory sounds become prominent and are the only ones heard with the exception of the obstructive borborygmi.

Various friction rubs may be heard in the presence of a fibroplastic exudate, when such exudate exists between the visceral and parietal peritoneum. It is important that the abdomen should be shaved when

such rubs are sought for. Splenic, hepatic and gastric friction rubs have been recorded by us.

So far as could be determined, the author was the first to describe the splashing sound associated with pneumohydroperitoneum. This was heard only once, in a case of perforated carcinoma of the stomach which presented a long fluid level and a large pneumoperitoneum under the x-ray. It was noted each time the patient hiccuped, and could be elicited by having him inhale deeply and then forcefully exhale. It resembles the tinkling splash heard in hydropneumothorax.

Coin sounds in the presence of pneumoperitoneum are of some diagnostic aid. When combined with auscultatory percussion and the scratching or rubbing sound tests, they can outline the free air in the peritoneal cavity more accurately than percussion alone.

In the presence of ascites, the transmission of a fluid wave on percussion is accompanied by a "double tap" sound. The two taps are due to the fact that the percussion sound wave travels through the ascitic fluid faster than the fluid wave, hence, the two tapping sounds appear very closely together. The "scratch and rub" tests are two other auscultatory methods which produce a sound that is easily transmitted through meteorism and pneumoperitoneum but not through solid or cystic tumors.

In extra-abdominal lesions such as coronary thrombosis, pneumonia, pleurisy, pericarditis and osteomyelitis, the intestinal sounds remain normal unless diminished by abstinence from food or the presence of fever. Renal colic and pyelitis rarely affect peristalsis.

In the traumatic abdomen we make it a practice to auscultate the four abdominal quadrants every hour and record the findings. An early return of normal sounds is reassuring that serious intra-peritoneal damage is not present. On the other hand, should the abdomen become quieter or silent, we believe that surgical intervention must be seriously considered. The abdomen should be auscultated both before and after reduction of a hernia. If the segment of intestine which has been reduced is viable, normal sounds reappear. When the abdomen remains quiet and becomes silent, one considers possible leakage from a reduced but nonviable piece of bowel and exploratory laparotomy is considered. If a hernia is reduced without relieving the obstruction, the so-called "reduction en bloc," the abdomen becomes silent or obstructive borborygmi appear.

### SUMMARY

1. The diagnostic value of abdominal auscultation has been emphasized, and its importance in the di-

agnosis of peritonitis, intestinal obstruction and abdominal bleeding is stressed. The coined phrase "the wetter they are the quieter they are" applies to spreading peritonitis, and aids one in following the course of such a condition. The presence or absence of intestinal sounds differentiates intra-intestinal from intra-peritoneal bleeding.

2. Normal and abnormal sounds are easily recognized with a little practice. This differentiation is elicited by tonal qualities, pitch, rate and intensity.

3. In diagnosing intestinal obstruction, the presence of obstructive borborygmi are pathognomonic. The metallic tinkling quality of these sounds has been fully described.

4. Other abnormal sounds which are found such as rubs, bruits, and succussion splashes are also noted.

### BIBLIOGRAPHY

1. Blumer, George: *Bedside Diagnosis*, Philadelphia, Saunders, 1938.
2. Boas, I. L.: *Diagnostik und Therapie der Magenkrankheiten*, Leipzig, G. Thieme, 1925, p. 70.
3. Cannon, W. B.: Auscultation of rhythmic sounds produced by stomach and intestines, *Am. J. Physiol.*, 14:339-353, 1905.

4. Carey, E. J.: Studies in structure and function of small intestine, *Anat. Rec.*, 21:189-215, 1921.
5. Charbonnier, A.: L'auscultation dans les affections chirurgicales aiguës de l'abdomen, *Rec. méd. de la Suisse rom.*, 56:513-585, 1936.
6. Da Costa, J. C.: *Physical Diagnosis*, ed. 4, Philadelphia, Saunders, 1919.
7. Dunner, L., and R. Neumann: *Perkussion, Auscultation und Palpation der Brust und Bauchorgane*, Vienna, Urban u. Schwarzenburg, 1924.
8. Ewart, W. A.: Note on auscultatory friction as an adjunct to auscultatory percussion in abdominal exploration, *Lancet*, 2:551, 1898.
9. Flint, A.: *Manual of Auscultation and Percussion*, Philadelphia, Lea & Febiger, 1912.
10. Lidsky, A. T.: Auscultation of abdominal cavity in diagnosis of acute surgical diseases, *Vestnik khit.*, 36: 56-57, 1934.
11. Nash, Joseph: *Surgical Physiology*, Springfield, Thomas, 1942.
12. Stevens, N. C.: Auscultation of abdomen; aid to diagnosis, *New England J. Med.*, 211:108-110, 1934.
13. Stevens, N. C.: Auscultation of the abdomen, *New England J. Med.*, 215:22-26 (July 2) 1936.
14. Vaughan, R. T., and P. Thorek: Abdominal auscultation, *Am. J. Surg.*, 45:230-234 (Aug.) 1939.
15. Watkins, T. J.: Abdominal palpation and auscultatory percussion, *Surg. Gynec. & Obst.*, 11:426-429, 1910.
16. Wangenstein, O. H.: In *Christopher's Textbook of Surgery*, Philadelphia, Saunders, 1936, p. 1210.

### New Application of Electronics

Irradiation by beams of highly accelerated electrons for ultrashort exposures has been found effective in the sterilization and preservation of a wide variety of biologic products. In a preliminary report recently published (*Science*, January 31, 1947) Arno Brasch and Wolfgang Huber have discussed their early results and indicated the possibilities to be explored in future work along the same lines.

They exposed drugs, foodstuffs, blood and cultures of micro-organisms to electronic intensities generated by a Capacitron of from 30,000 to 50,000 amperes for a time period of about 1/1,000,000 of a second. With one, or a few such exposures, they were able to preserve a number of raw foodstuffs without noticeable changes in appearance, taste or odor. An irradiated steak, for instance, was unchanged for all practical purposes after storage in the incubator at 37.5° C. for 12 days. Whole eggs gave similar results and even sea foods could be stored at elevated temperatures after irradiation. It is thought that the effective mechanism is the destruction or inhibition of enzyme systems by the electronic irradiation.

Sterilization of contaminated raw food or cultures of micro-organisms was accomplished more easily than

preservation. Brasch and Huber found that the doses necessary for sterilization caused no detectable morphologic changes in the bacteria. These and other results lead them to believe that this type of radiation can be adapted to serve as a satisfactory tool for the attenuation of bacteria in a graded and rigidly controllable way.

Because highly accelerated electrons release more intensity below the surface and have a well-defined penetration range they are ideally suited to the demands of radiation therapy. The biologic intensity of penetrating electrons is about 500,000 to 1,000,000 times greater than that obtainable with x-rays. It is possible to deliver through very small evacuated channels, injection needles for instance, enough radiation intensity for effective therapy in tumors lying far below the surface, and without harming the overlying or surrounding tissue. Such tumor eradication was actually accomplished with rabbits.

A great deal of exploratory and developmental work remains to be done, and it is possible that the operating costs of such an elaborate device as the Capacitron may limit the application of this new technic.

# Cases from the Medical Grand Rounds of the Massachusetts General Hospital

JAMES H. MEANS, M.D., Chief of Medical Services

Edited by LEWIS K. DAHL, M.D.

BOSTON, MASSACHUSETTS

## CASE 6

### HYPERTENSIVE ENCEPHALOPATHY

DR. PAUL D. WHITE: This case illustrates the advantage of having almost all the services represented in a hospital. I have always been thankful that we have children in this general hospital, and I think that the Children's Service is probably grateful that they are associated with adult medicine. We are lucky to have had this next patient, because he is a little over the age at which he would have entered the Children's Service, where he has been before.

DR. J. H. DONALD: Patrick C., No. 479575, is a 13-year-old boy who entered by way of the Emergency Ward for the second time about ten days ago, with convulsions. His first admission to this hospital was on the Children's Medical Service about 22 months ago, at which time he was studied and the diagnosis of chronic glomerulonephritis was made. He was subjected to bilateral sympathectomy, and biopsies of each kidney at the time confirmed the diagnosis.

Following a hospital stay of two or three months, he was discharged and since has improved somewhat with slight lowering of the blood pressure. Recently he has been active, going to school and living a fairly normal life. He was last seen in this hospital in the Children's Medical Outpatient Clinic on October 10, with status as shown on the chart (Table 1, Col. II). Column I shows the studies at the time of his admission prior to sympathectomy.

On the evening he came in, his story went back three weeks when he had developed an upper respiratory infection. Over the preceding five days he had had a mild headache in the evening, either frontal or occipital, readily controlled by aspirin. On the evening of admission this headache appeared at the usual time of about six-thirty and did not respond to aspirin. By eight, it was quite severe. Shortly before ten o'clock in the evening he complained of nausea and very soon thereafter had a generalized convulsion with unconsciousness and vomiting. He was taken to

TABLE 1

	MARCH 1945	OCT. 1946	DEC. 1946
Av. B.P.	140/90	150/115	160/120
Total Protein	3.8 Gm.	5.0 Gm.	3.9 Gm.
B.U.N.	11.9 mg.		
Urea Clearance	61+69%		
P.S.P. (2 hours)	67%		34%
Cholesterol	500 mg.		325 mg.
Na	140 m.eq./l.		136.8 m.eq./l.
Cl	100 m.eq./l.		110 m.eq./l.
Ca	9.4 mg. %	7.2 mg. %	8.1 mg. %
P	5.2 mg. %	5.5 mg. %	5.5 mg. %
NPN		36 mg. %	60 mg. %
ECG	SI, $\nearrow$ P-R		
Eyes	Grade 0		

another hospital, there had a more severe convulsion, and because of his previous attachment with this hospital was referred here. During the time of transport he had been able to recognize his father and speak to him.

When seen in the Emergency Ward he was a well developed, moderately well nourished young boy who was varyingly responsive, and highly irritable. At other times he was unresponsive. He was incontinent and retching. His pupils were open, clear and reacted promptly; the fundi showed 1.5 to 2 diopters of papilledema. The neck was supple. The lungs were clear. The heart was 1.5 cm. outside the midclavicular line. A2 was louder than P2, although both were increased. There was a suggestion of a gallop. Blood pressure was 230/180-190. The abdomen was essentially normal.

He was given magnesium sulfate, using our stock solution of 50 per cent magnesium sulfate. We chose the intramuscular route of administration. He received 3.0 Gm. at 2 A.M. followed in 45 minutes by 2.0 Gm. Total dosage was slightly over the 0.4 cc. of 25 per cent solution per kilogram, which is the working rule of thumb for hypertensive encephalopathy. His response is dramatically shown by the blood pressure chart (Fig. 1). His clinical condition was closely similar and by eight o'clock in the morning of admis-

## Massachusetts General Hospital

NAME Patrick G. # 479575

DATE 12/3/46

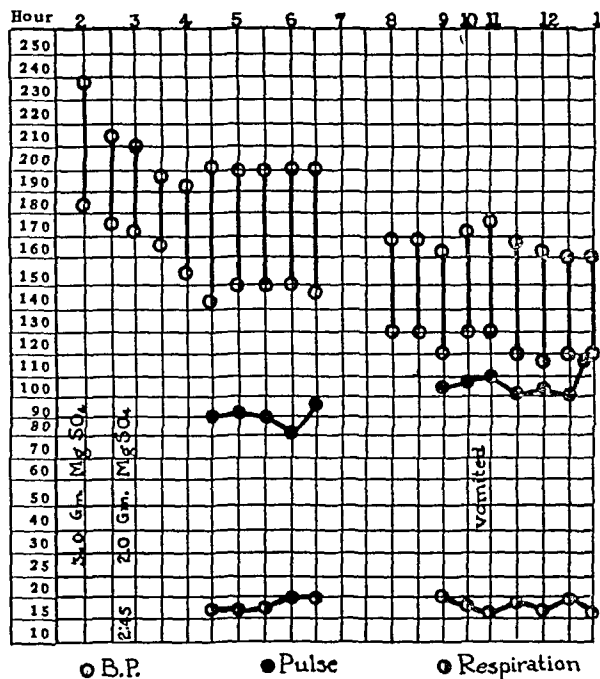


FIGURE 1

sion he was responsive and felt remarkably well. The papilledema had already begun to subside and by the second hospital day was hard to measure; there was just a suggestive blurring of the disk bilaterally. His urine showed just what it had in the past, 4 plus albumen with occasional red and white cells and heavy granular and hyaline casts. We had expected a fresh shower of red blood cells indicating, perhaps, a flare-up of his glomerulonephritis, but in repeated examinations none was found. You can see the repeated studies done on this admission and compare them, showing the course of his illness (Col. III, Table 1).

DR. WHITE: You might have him come in. He is in very good condition now. He says he feels perfectly well and yet he was, of course, very seriously ill on entrance and I want to congratulate Dr. Donald on his emergency therapy. And I am sure he appreciated what Dr. Butler had advised because he took this treatment directly from some lecture by Dr. Butler. This is the lad who is now feeling quite well, he told me this morning (indicating). No headaches, and his blood pressure—what is his present reading?

DR. DONALD: It averages about 160/120 now.

DR. WHITE: How are your eyes? Can you see well now?

Patient: Yes, I can see.

A PHYSICIAN: Will Dr. Donald read the dosage again?

DR. DONALD: 0.4 of a cc. of 25 per cent solution per kilogram.

DR. WHITE: Here is a severe hypertensive crisis from which this lad is recovering. I would appreciate very much if Dr. Butler will tell us about his previous knowledge of this boy and what he thinks of him now and what he would advise.

DR. ALLAN M. BUTLER: I am glad of the opportunity to review this case here in order to bring me up to date on this patient who has been on the Children's Medical Service. You may wonder why bilateral sympathectomy was done on a child who had a diagnosis of subacute or chronic glomerulonephritis. Those who saw this boy on our service believed that his primary hazard was one of progressing hypertension rather than one of progressing renal insufficiency. Therefore, the way to modify the course of the disease, which was almost sure to be rapidly progressive and fatal in a youngster with this degree of hypertension, was deemed to be sympathectomy. So Dr. Smithwick was called in and he agreed that the best way to stop the progression of this condition in this young man was bilateral sympathectomy. We have done this in other cases and we have given, we feel, several years of relatively happy life to such patients, even though the renal disease, of course, progressed. Now on this youngster we had kidney biopsies at the time of the sympathectomies and Dr. Castleman and I reviewed those sections this morning. I think Dr. Castleman would agree that the pathologic condition of the kidneys was not, perhaps, the major part of this boy's hazard. They revealed a very spotty type of glomerular involvement, with many glomeruli perfectly normal and only a moderate change in the vessels of the kidney. Is that right, Dr. Castleman?

DR. BENJAMIN CASTLEMAN: Practically none.

DR. BUTLER: There was some question, after examination of the specimen, as to whether there may have been a little element of infection. The specimen being from the cortex, did not go very far down in the pyramids and, perhaps, wasn't too satisfactory in this respect. So much for why we did the bilateral sympathectomy. I think we will do it again in similar cases.

Now, as regards the treatment of a cerebral crisis. I think we would have given this boy magnesium sulfate intravenously rather than intramuscularly. This boy's response to the amount of magnesium sulfate given intramuscularly was very fortunate. Usually we give somewhere around 200 mg. per kilo intravenously and repeat it if necessary in about four

hours, watching for signs of too high a magnesium level in the serum: namely, the changing of reflexes, too abrupt fall in blood pressure, flushing of the skin, nausea, and alteration in respiration. We hardly ever encounter any of these symptoms other than some nausea and vomiting when the magnesium is given too rapidly. Such therapy frequently stops the course of the hypertensive cerebral episode.

DR. WHITE: How soon? At once?

DR. BUTLER: Almost immediately if you push your therapy to the point of raising the serum magnesium from the normal level of 1.5 or 2 to 6 or 8 m.eq./l. It is not a therapy that is 100 per cent successful, but in our experience it is perhaps one of the most effective ways to stop a hypertensive crisis.

DR. MAURICE FREMONT-SMITH: Where does that magnesium work?

DR. BUTLER: Supposedly it works by causing peripheral dilatation of the smaller arterioles throughout the body and in that manner relieves the vascular spasm thus improving the circulation generally and particularly cerebrally.

The next question is what are we going to do now with this boy, who has had a progression of his nephritis. Now we are faced with diminishing renal function as well as hypertension. His NPN and serum inorganic phosphorus are elevated. Though his total serum calcium is low, the ionized calcium is not markedly diminished because his serum protein is diminished enough to cause diminution in protein bound calcium. We are not going to help his renal insufficiency. We can modify his regime as to intake of water, calcium, sodium chloride, potassium, and protein so as to adjust his metabolic demands to his renal condition, but that is all you can do therapeutically for a fellow with progressive nephritis. But again he comes in because of the hypertensive element of his disease. I should think, having started on this course of hypertensive sympathectomy, one would have to consider whether you want to extend the original operation. The original operation apparently had almost no effect in disturbing his circulation when he changed from the lying to the upright position. So one wonders whether we have not quite a little leeway in extending the sympathectomy and could go a little lower and perhaps gain a temporary benefit by again controlling the degree of the hypertension or at least the hypertensive symptoms. You would know more about that than I, Dr. White.

DR. WHITE: Thank you very much, Dr. Butler. I am sure that last point is still to be proved one way or the other. Dr. Butler, can you explain why he had the hypertensive crisis this time? We find no evidence of new renal infection.

DR. BUTLER: No, I don't think I can. I don't think we know why any of these youngsters have such a hypertension.

DR. WHITE: Doesn't occasionally an acute renal infection set off a crisis?

DR. BUTLER: Yes, it may; and it has been looked for and not found to be present. If he came in with a renal infection I should think one would be much more optimistic in doing something for him than one is now.

DR. WHITE: Do you want to add any comment about the biopsy, Dr. Castleman?

DR. CASTLEMAN: I looked at the slide this morning and found about half of the glomeruli in the kidney perfectly normal. Without knowing anything about the story, one would not ordinarily think of a chronic glomerulonephritis, because, by and large, when you see a case, at least at autopsy, every single glomerulus is involved. This brings up the question whether this disease starts as a focal glomerular nephritis unlike the acute form where all the corpuscles we know are involved. The chronic disease may be a different type of disease that may start as a focal disease and spread to other glomeruli. In a few places some of the glomeruli look like ones occasionally seen in disseminated lupus erythematosus. It has not the characteristic crescents that you like to see in the ordinary case of chronic glomerulonephritis. All the proliferation is intracapillary rather than between the capsule and the tuft.

DR. WHITE: Thank you. Any other questions or discussion?

DR. BERNARD M. JACOBSON: What would happen if you injected amyl nitrate at the time of the crisis?

DR. BUTLER: It might help. We have done that on several patients, but we were not too pleased with the benefit.

## CASE 7

### MULTIPLE MYELOMA

DR. WALTER BAUER: The case to be shown this morning is one of interest for two reasons. One, at the time of entry there was some question as to the exact diagnosis, and two, once it was established, a new form of therapy was instituted despite the fact that the disease was far advanced and there seemed very little likelihood that any therapy could be effective at that time. We reasoned that if it was what we thought, this particular case would be of considerably more value than if the symptoms had been less disabling. Dr. Mellinger will present the case of Mr. S. aged 48, who came in because of skeletal pain.

DR. GEORGE W. MELLINGER: Mr. S., No. 552378, was



symptom free as far as his skeletal system goes until 13 months before admission. At that time he began to have dull aching pains in the region of the costal margin sometimes on the right and sometimes on the left. These pains were made somewhat worse by respiration and they would come on for several days at a time and then go away. At about the same time, he had a pain in the sacro-iliac region which was made worse by coughing, sneezing, and straining. Because these pains continued he went to his local doctor, who made a diagnosis of pleurisy on the basis of the chest pain and prescribed codeine and aspirin, which relieved the pain completely. However, the pains recurred off and on until April 1946 at which time the chest pain almost entirely stopped. He had only occasional chest pains, but had the sacro-iliac pain continuously. At the same time he began to have another pain in his back, separate from the sacro-iliac pain, which was worse on motion.

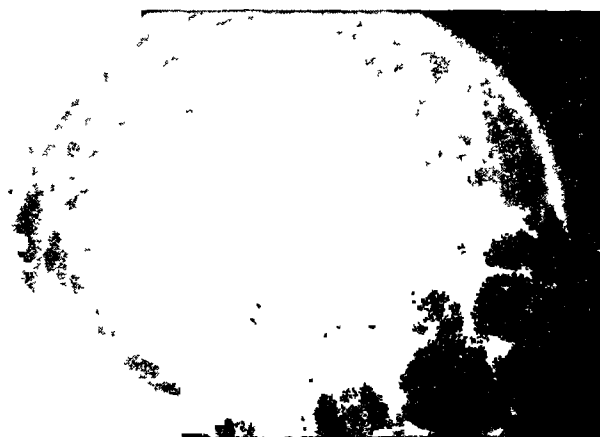


FIGURE 2

In August 1946 he went to another hospital because of the pains. Here no specific therapy was instituted and he was discharged after about a week and a half. A month and a half before admission he entered still another hospital because of the pains. There a gastro-intestinal series showed an active duodenal ulcer, after which he was started on an ulcer regime and then discharged.

Following this he continued to have dull pains in the anterior chest and sacro-iliac region and also, in addition, epigastric fullness. He had vomited three times prior to his admission here, the last time having been a week before admission and the vomitus was tinged with blood. The other times were several months before admission and there was no blood.

The past history reveals very little disease. In January 1945 he had "blood poisoning" and was treated

and cured with sulfonamide therapy. He also had the usual childhood diseases. The family history was essentially negative.

He was admitted to this hospital on November 15, 1946. Physical examination at that time revealed a well developed, rather poorly nourished white male in no acute distress. The chest was essentially negative. There was only minimal tenderness over all the ribs. There was no tenderness in the spine. The heart was slightly enlarged. There was a soft systolic mitral murmur, heard best at the apex with an occasional extrasystole. The spine in the thoracic region was slightly stiff and the lumbar region seemed not mobile at all. The liver was not palpable but percussed one or two fingersbreadth below the costal margin. Otherwise the physical examination was essentially negative.

As for the laboratory work, the urine showed a specific gravity of 1.015 with one plus albumen; no sugar; there were about 10 white cells per high power field, with many hyaline and granular casts. The white count was 8,600, red count 2.9 million, hemoglobin 9 Gm., differential count normal with 65 per cent polymorphonuclears. The stool was brown, formed and guaic negative.

At this time we made a diagnosis of rheumatoid spondylitis. He was seen by one member of the Arthritic Clinic who agreed with that diagnosis, but when he was seen on the Arthritic Rounds, that group believed that the amount of asthenia and anemia was out of line with the diagnosis and suggested that the Service investigate malignancy and multiple myeloma. Subsequent chemistries are as follows: Total protein in one case 12.1 Gm., in another 11.4 Gm., at which time the albumen was 2 Gm. and the globulin 9.4 Gm., being of course, almost diagnostic of multiple myeloma. The nonprotein nitrogen was 70 mg. per cent; creatinine 2.6 mg. per cent; uric acid 5 mg. per cent; phosphorus 4.3 mg. per cent; alkaline phosphatase was 4 units and the acid phosphatase 1 unit. Blood Hinton was negative. A congo red test showed 52 per cent retention of the dye in the serum at the end of one hour which is in the borderline range of abnormality according to present concepts of the Arthritic Group here. Phenolsulphonthalein was excreted poorly, between 10 per cent and 15 per cent in two hours. That was repeated and confirmed. A corrected sedimentation rate was 1.85 mm./min. 17-Ketosteroids were 4.6 mg./24 hours.

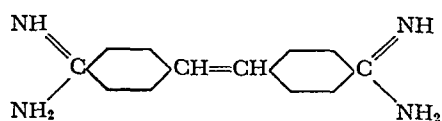
At this point Dr. Jacobson did a sternal puncture. The smear showed 30 per cent of the white cells to be either plasma cells or plasmablasts. At this time a positive diagnosis of multiple myeloma was made.

X-ray examination of the skull showed multiple peppered areas of decreased density consistent with multiple myeloma or metastatic malignancy. X-rays of the chest showed the chest to be negative with the exception of the enlarged heart and some pulmonary congestion. X-rays of the spine revealed a honey-combed appearance throughout the entire spine and, in addition, large areas of decalcification in the sixth cervical spine, and sixth and eighth thoracic spine showed compression fractures. There was a large area of bone destruction in the right sacro-iliac region.

Shortly after admission, about November 23, the patient began to have pain in the region of the ribs. On admission he had slight pain on motion of the spine and that gradually increased up to the 17th day, at which time he had very severe pain even with no motion. At about that time demerol was started, approximately 100 mg. a day. That was given PRN. At about the 23rd day the pain was becoming worse and he got more demerol, in the neighborhood of 300 mg. per day. On the 34th day he was having so much pain that we changed to morphine, in spite of the fact that we were using another medicine, which we will tell you about in a minute.

On December 7 we started a new drug, stilbamidine, of which you see the formula in Figure 3 and which

4:4 Diamidino stilbene



Diethylstilbestrol

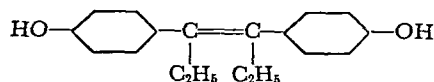


FIGURE 3

Dr. Jacobson is going to discuss. We started this therapy at his suggestion. The patient received 50 mg. intravenously every two days. At first this produced no effect but after about a week or a week and a half we began to notice that he was having less pain with no increase in medication, so we decided to stop the medication of morphine at that time entirely. We did, and for the past week he has had very little pain. He has sort of a dull aching pain in his ribs and spine but we can move him around very comfortably.

DR. BAUER: We will show his x-rays before the patient comes in. I think it is only fair to say that at the time he was seen in the Arthritic Clinic, in addition to the other things that embarrassed us, was the

fact that this man appeared much more malnourished and had more evidence of asthenia and anemia than one would ordinarily expect on the basis of a rheumatoid spondylitis. His pain had been unrelieved even to a slight degree by any of the usual medications employed and on physical examination that day the rather exquisite tenderness of the sternum and ribs and even the pelvic bones was demonstrable very readily. It was largely on the basis of the latter that the group suggested the possibility of some type of malignant disease, more likely multiple myeloma, because of the physical examination pointing to widespread bone marrow involvement. You will note that he has the rather characteristic changes of multiple myeloma of the skull. He has many areas of destruction. They are likewise demonstrable in the pelvis and as Dr. Mellinger says, there is evidence of a compression fracture of the sixth and eighth dorsal vertebrae.

I think the thing that is really impressive about Mr. S. is that despite medication, whether it was demerol or morphine, he was still very uncomfortable, and I am sure that Dr. Jacobson felt, as I do, that it was a very unfair case to test a new therapeutic agent. We believed that the situation could not be altered and yet, much to our surprise after a total of 11 such injections we have an individual who complains very little of pain, does move from side to side, and has much less tenderness of the skeletal system on pressure.

It is also of interest that when he came in he had considerable bleeding of the lips and that too has disappeared. He is eating much better and he has less pain when I press his ribs this morning. Pressure of that degree some weeks ago was extremely painful to the patient. So I think there can be little doubt about the fact that the patient is considerably better. He agrees with that.

Now, Dr. Jacobson requested permission to try stilbamidine on this patient. He will next tell us about what is known of the use of this drug in multiple myeloma and why it was first employed. Dr. Jacobson.

DR. BERNARD M. JACOBSON: After seeing about 45 cases of histologically proved multiple myeloma in the last 12 years, I never thought I would live to see the day when someone reported a drug which would do any good in this extremely malignant disease. In 1939, Dr. Ewins of the pharmaceutical firm of May and Baker in London synthesized a series of compounds which were related to synthalin. That was a drug, as you possibly remember, given orally in the treatment of diabetes. It has some blood-sugar-lowering principle. Dr. Ewins synthesized a series of drugs for the experimental treatment of certain para-

sitic infections. In 1939, Lourie and Yorke in England tried a series of aromatic diamidines in experimental trypanosomiasis and leishmaniasis and they found that of this series of diamidine drugs the material called stilbamidine had a very remarkable effect in experimental trypanosomiasis. I have put the formula of diethylstilbesterol on the board (Fig. 3) just to show the relationship. It is only vaguely chemically related to stilbamidine. I might add that in my search of the literature I have found no reference to the use of stilbamidine as an estrogen. Stilbamidine is 4:4 diamidino stilbene.

After the work of Lourie and Yorke in 1939, the material was taken up by clinical investigators in East Africa and since then it has been established that stilbamidine is a very effective drug in leishmaniasis. It is fairly effective in trypanosomiasis, often effective in certain cases of malaria.

The work with multiple myeloma was completely originated by Dr. Snapper of the Mt. Sinai Hospital in New York. I had heard of this work of his several months ago, but his first publication was in the September-October number of the *Journal of Mt. Sinai Hospital* in which he says the following; and this is apparently all we will know about the reason for the application of this drug in myeloma:

"Stilbamidine is a drug which in recent years has been used with great success in the treatment of kala azar. This disease is characterized by an increase of the globulin content of the serum. Since the globulin content of the serum is also frequently increased in multiple myeloma, we have tried stilbamidine since the beginning of 1945 for the treatment of multiple myeloma."

Now to the date of publication of this paper Dr. Snapper had treated a total of 14 cases, the longest ones over a period of 16 months. Of the 14 cases, five have died and nine are living. Of the nine cases as far as I can gather from this article, all the cases have shown a moderate to complete regression of bone pain and many of them have resumed their normal occupation and are considered to be in remission. Now, the improvement, in his experience, did not come until after the fifth or sixth injection of the drug given every other day or every third day. Improvement was first manifested purely symptomatically. According to one statement of his, there is no effect of this drug on the abnormal serum globulin nor does it seem to eradicate the disease from the bone marrow. On the other hand, there are some very remarkable changes portrayed by Dr. Snapper in x-rays, before and after the treatment; in several cases with recalcification of punched-out areas and healing of pathologic frac-

tures. After about four weeks of treatment he has noted in practically all cases significant cytologic change in the plasma cells of the bone marrow and this change is the only objective finding so far that takes place with this treatment, in addition to the x-ray changes.

Now, the plasma cell in a typical multiple myeloma is a moderately large cell with a nucleus that is usually slightly eccentric and usually with a little halo around the inner part of the nucleus. The stained cytoplasm is either light or dark blue. Once in a while you will see an azurophilic inclusion body but for all practical purposes it never contains granules. The change Dr. Snapper describes is the appearance, after four weeks or so, of rather dense basophilic granules in the plasma. In an article published in the November 1946 number of *Blood* he pictures these inclusion bodies or granules appearing in the cytoplasm of these cells. He states that 80 or 90 per cent of the plasma cells develop these granules.

To date we have treated Mr. S. with stilbamidine, 150 mg. of the drug put into solution in 10 cc. of normal saline, injected slowly intravenously. There have been no serious untoward reactions. Dr. Isaac Taylor, who is working with me on this problem, has given all the injections himself, and with the exception of one injection, there have been no significant toxic symptoms. Nausea, vomiting, falling blood pressure, sweating, and other evidences of stimulation of the parasympathetic nervous system were reported in the past and have been seen by us on one occasion in this patient. A late result of the drug is stated to be a dissociated anesthesia of the trigeminal nerve on one side or other, where sensation to touch is lost, but heat, pain, and temperature sensation is retained. That, however, is said to come only several months after beginning treatment. Dr. Snapper at first used ten injections, 150 mg. apiece, as a course of treatment. He derived that figure from the results in leishmaniasis. With the majority of natives affected with this disease, ten injections apparently cured them. On the other hand, with other cases Dr. Snapper has continued the injections to 15 or 20, up to even a total of 5 Gm. of the drug before ceasing. From December 7 to December 28, we have given Mr. S. a total of eleven injections and we plan to continue this dosage for the present.

Now, I have done my best to be as objective as possible and I have relied to a large extent upon the Ward Service and the Arthritic Group for an evaluation of the results. I guess we all agree there has been symptomatic improvement in the patient as far as pain goes. There has been a very definite improve-

ment in general nutrition. His appetite and desire to live seem to have improved in the past week or so. We know a patient with multiple myeloma can have spontaneous remissions for weeks or months as far as pain goes. We plan in another week or so, after a few more injections, to repeat the sternal puncture and see if this granulation has developed in the plasma cells. Later studies of the serum globulin will be of interest. This patient so far as we have observed has not put out any Bence-Jones protein. He has a slight degree of renal insufficiency and his NPN is 55-70 mg. per cent. It is probable that he has some Bence-Jones protein in the tubules of the kidneys.

Dr. Snapper makes the statement that in the presence of renal insufficiency treatment should be guarded.

DR. JAMES H. MEANS: Did Dr. Snapper report any change in the blood picture in the anemia that he saw, Dr. Jacobson, in any of these cases?

DR. JACOBSON: No mention at all of changes in the hemoglobin status. He states that the serum globulin seems to be unchanged.

DR. MEANS: It seems to me it is an amazing thing, because in this parasitic disease you mention, the drug acts by being antagonistic to the parasite. Why on earth should it be effective in this disease which we don't think of as a parasitic disease? The only point in common apparently is a high globulin and the drug does not affect the globulin. It is all a complete mystery to me and very confusing.

DR. CHARLES L. SHORT: It has a chemical action on some component of the plasma cell. Doesn't Dr. Snapper mention that?

DR. JACOBSON: There is some work with stilbamide to show it can liberate protamines from protamine ribonucleate and he thinks that these granulations which appear consist of ribose nucleic acid and may indicate that the plasma cells are inhibited in their survival.

I would like to repeat there are only two objective findings that Dr. Snapper mentions. One is the appearance of the granulations in the plasma cells and the second the changes in the x-ray.

DR. MEANS: Is there any increase in plasma cells? Can you make any sense out of this behavior of the two entirely different diseases?

DR. JACOBSON: No, sir.

DR. MEANS: They are similar in no way except they both have a high globulin and the drug doesn't work on the high globulin.

DR. BAUER: In a lot of diseases with high globulin it might be tried.

DR. JACOBSON: I might also mention that Dr. Snapper has one little line to state that this drug has been tried in carcinoma, lymphoma, leukemia, and granuloma inguinale.

DR. MEANS: Could I say one thing about the diagnosis of this disease? One will never make it unless one thinks of it and one does not think of it very often, because it is a rare disease. But, when a case of this type is shown, I always like to recall an episode in which we had a patient in the ward with a totally obscure condition. He was awfully sick and nobody had the foggiest idea what was the matter with him until one of the fourth year medical students, entirely on his own initiative, made such a careful blood study that he found plasma cells in the peripheral blood and that led to the diagnosis of multiple myeloma. I throw that out to encourage the fourth year men to make very careful blood studies.

DR. ARLIE V. BOCK: It is possible to have death from this disease with little or no evidence of x-ray involvement.

DR. BAUER: Yes, but not until after the postmortem, when he reviews the films, is the radiologist willing to state that he missed the lesions which he had previously thought were negative. Even under those circumstances we have had at least one patient here in whom the x-ray men would not commit themselves after the postmortem.

## CASE 8

### ERYTHEMA MULTIFORME

DR. PAUL D. WHITE: Before showing this case, I would like to make a remark or two. We internists, whether we are primarily interested in special organs or systems or in the more general field of internal medicine, have the disadvantage in this hospital, and in many other hospitals I am sure, in not seeing all the diseases of importance that do occur. We skip to a large extent dermatologic conditions, for example, and we don't take patients with contagious diseases and tuberculosis, which I think would be to our advantage to have. We do have, on the other hand, the advantages of a large general hospital with its many special groups, including the Eye and Ear Infirmary, with the eye, ear, nose and throat services, the psychiatric ward, the surgeons and pediatricians, and still other groups with whom we can constantly confer. I am sure that most of us working in special fields in such a large hospital appreciate these contacts and would decry the establishment of special institutions for the study of any one disease or any one organ when such an organization as this hospital of ours is possible. Small hospitals have been drawn of late

into the larger hospitals and we too have taken to our growing and mutual advantage a number of small hospitals as part of our medical community. When the beautiful new Institute of Cardiology was established in Mexico City not long ago, with its fine organization and equipment, I somewhat doubted the wisdom of such a move. If, however, they can have very close to them general clinics and special clinics and laboratories of every sort, they may escape the danger that is inherent in a special group working geographically by itself. Here, of course, in this large general hospital with surgeons and internists and members of all the groups working together, we have a great advantage.

It is well for us now and then to pause to see and discuss some patient who has an important disease, but who falls somewhat out of our usual scope. And that is the type of patient we shall present this morning. Dr. Craige.

DR. ERNEST CRAIGE: This is Mr. St. J., No. 71903, a 41-year-old tile maker, who was admitted to the East Medical Service on November 30, 1946 complaining of chilly sensations, fever, and skin rash of four days' duration.

He was first seen in this hospital 13 years ago when he was studied for a traumatic condition of his right chest. At that time routine chest examination by x-ray showed several circular areas which were interpreted as being consistent with the diagnosis of lymphosarcoma. No peripheral node was available for biopsy, but he was given 600 R spray radiation and over a period of six months there was gradual resolution of the lesions.



FIGURE 4

More than four years ago he had a recurrence of the same trouble and again spray radiation was directed at the mediastinum with a slow disappearance of the nodules.

Subsequently the patient was followed in Tumor Clinic where increasing doubt was cast on the original diagnosis. In 1941 he was suddenly stricken with chilly sensations and fever, with sore throat, difficulty in swallowing, and the cough which he had had for many years became suddenly much more productive and yielded several cupsful of purulent, bloody sputum daily. Following these symptoms, he noticed the appearance of a rash which was located in his trunk, extremities, penis, buttocks, and chest. This was accompanied by a most severe stomatitis and conjunctivitis.

He was admitted to the Skin Ward where it was found that the lesions on his skin were oval in shape with erythematous raised borders and bullous centers, which were characteristic of erythema multiforme bullosum. For a while the diagnosis of pemphigus also was entertained, but this was discarded. The patient was acutely ill, with temperature of 104°, and his course was complicated by bronchial pneumonia. He was treated with sulfathiazol and intravenous fluids, and after two months was discharged, but with some of the skin lesions still present.

At the time of discharge his eyes were severely injured, the conjunctivitis having gone on to scarring and symblepharon, and he had almost lost the sight of his right eye. He was followed after this in the Tumor Clinic and also in the Pulmonary Clinic where, because of his chronic cough, it was thought advisable to make bronchograms. These showed bronchiectasis in the right and left lower lobe, but surgery was not thought advisable.

After this the patient continued at work, and except for two minor exacerbations of his skin condition, was fairly well until about November 22, 1946. Then again he was stricken with chilly sensations and fever and all the series of symptoms he had reported before. These were severe sore throat, difficulty in swallowing, increase in his cough, production of bloody sputum, and again the same rash, although limited this time to his hands and feet, his forearms, penis and buttocks; and again there was severe conjunctivitis and stomatitis. His mouth was covered with hemorrhagic ulcerated areas over which there was a gray pseudo-membrane. His temperature was 102° and he was acutely ill, although apparently not as ill as at the previous admission.

Penicillin had been given on the outside, 40,000 units every three hours for three days, and this was continued in the hospital. Bacteriologic studies yielded only *Hemophilus influenza*, whereas at the previous admission Type 9 pneumococci and beta hemolytic streptococci had been cultured from the sputum.

In the hospital the patient's course has been satisfactory. His temperature has fallen to normal over a four-day period on penicillin and he has had a satisfactory regression in his skin and mouth lesions. We have three slides which show him as he was at his previous admission and again at this admission.

DR. WHITE: He has greatly improved but still shows many of the lesions with which he entered the hospital. We believe that the reason why we were lucky enough to get him instead of his going to the Skin Ward was that he had enough secondary infection to make him seriously ill on entrance. The role of the penicillin, I believe, unless Dr. Swartz disagrees with me, has been that of control of the secondary infection. The sputum changed from purulent to watery and his temperature came down. We doubt, however, whether the penicillin has actually controlled the underlying condition about which Dr. Swartz will speak later. (Patient brought in.) You see he dreads the light. He still has considerable photophobia and his eyes bother him a great deal; otherwise he is much more comfortable than he was originally. Will you put your tongue out? You can still see the lesions on both sides of the swollen tongue, as evidence of the rather intensive stomatitis that he had on entrance (Fig. 4). On his hands you can also see remains of the lesions. They were much redder with whitish centers when he first came in. They are drying up without, I think, having become purulent (Fig. 5). He has other lesions on his arms and especially over the buttocks, on the penis, and on the soles of the feet, but much less than on his hands. He tells me that he doesn't feel too badly today. He is certainly quite a changed man from the time of his entrance some days ago.

Now may we have the lantern slides. This photograph was made at the time of his last admission to the hospital and shows more extensive involvement of the skin of the trunk and extremities than he has shown on this admission. This time there have been only a few lesions over the trunk, mostly on the buttocks and considerably on the palms and soles; the involvement of the mucous membranes of his mouth and throat and that of his eyes have been the chief problem.

I would like to call on Dr. Swartz to speak from his experience about this condition, erythema multiforme, or whatever he may want to call it. We don't ourselves think that the terms which have been used are very satisfactory, but perhaps Dr. Swartz will explain.

DR. JACOB H. SWARTZ: I examined this patient yesterday and on examination then he showed residual lesions of what we dermatologists are accustomed to

call erythema multiforme. Going through the literature we find that this entity is described under various names, depending upon the physical findings, particularly of the skin and mucous membrane. In this instance, the medical men have sinned as much as the dermatologists by making classifications according to a little variation in the findings. I don't think, personally, that the entity known as Stevens-Johnson disease merits that name, because it is merely a variation of erythema multiforme. It is simply a severe variety. I looked up the original article and the proponents claimed that the reason they made it a different entity was because the constitutional symptoms were more severe. The skin findings and particularly the mucous membrane and ocular findings were milder in erythema multiforme.

Erythema multiforme varies in severity and extent of involvement. This patient, whom I examined yesterday, had a very severe attack with all the findings of severe erythema multiforme in 1941, and had mild attacks about twice a year, varying from skin lesions only, to mucous membrane and ocular involvement. This, I believe, refutes the claim of Stevens and Johnson. They also claim it is a disease most frequently seen in male adults. The severest cases I have seen (and fatal ones) have been in a woman of 60 and in another in the early 30's. I therefore would like to call this disease erythema multiforme with varying severity.

A word about etiology. We can say there is no known etiology, but I would like to theorize a little and perhaps have grounds for so doing. I believe that this disease can fall in the group of diseases



FIGURE 5

known as disseminated lupus erythematosus, dermatomyositis, scleroderma, periarteritis nodosa, etc. The precipitating agent varies. We will find in some cases that it is the result of bacterial sensitivity with a focus

of infection somewhere. Those are the cases which have been reported helped with penicillin or other antibiotics. The worst case I have seen and one which was fatal, was the result of drug sensitivity (barbiturates). In a certain group of cases we cannot find any cause. I believe, however, that if we hunt long enough we may be able to find that there is either bacteriologic or drug sensitivity or a combination of both.

As to prognosis, the literature has it that practically all cases get well. I would like to disagree. In my experience of 25 years I recall at least two fatal cases. The prognosis in this disease should be guarded. The first attack may be mild and the second fatal. There is a tendency to recurrence.

There is no specific treatment, but if we suspect or can prove a possible bacteriologic sensitivity with possible focus of infection, then an attempt should be made to treat such cases. It will explain, perhaps, why some of the cases are reported cured with the various chemotherapeutics. The history as to drug sensitivity is very important.

I would like to emphasize these points before I stop: (1) That Stevens-Johnson disease is only a variant of erythema multiforme; (2) that any age and sex, not only young males, may be subject to this affliction; (3) that fatalities do occur; and (4) that bacteriologic and drug sensitivity play an important part as etiologic agents in a fair number of these cases.

DR. WHITE: Thank you, Dr. Swartz. Do you believe that the lesions penetrate down to the bronchi or stop before reaching there?

DR. SWARTZ: We had one postmortem that showed lesions down toward the esophagus as well as the bronchial tubes.

DR. WHITE: You think the reaction to penicillin was due to the control of secondary infection?

DR. SWARTZ: I don't think one can prove it, Dr. White, but, as I said before, personally I feel he may have some bacteria from his bronchiectasis to which he happened to have a sensitivity. It may be far-fetched, but very often for some reasons he reacts to that severely or mildly, and in this particular instance you clear up some of those bacteria and you help him.

DR. WHITE: Dr. Donald brought over this copy of the *American Journal of Diseases of Children* [24:526 (Dec.) 1922], containing the article entitled "A New Eruptive Fever Associated with Stomatitis and Ophthalmia, Report of Two Cases in Children," to which Dr. Swartz has referred. This article reports two cases of the so-called Stevens-Johnson disease in children. I am glad that Dr. Swartz has spoken as he has about the needlessness of labelling this as a new type

of disease. Dr. Weisberger will speak now on the oral lesions, and finally Dr. Mills about the eyes.

DR. DAVID WEISBERGER: My main interest is the mouth, but I occasionally look at the skin. It is very difficult to point out any mouth lesion that is characteristic of any disease, because it may seem to show a specific lesion and shortly after that have secondary infection.

DR. SWARTZ: Some of the so-called cured cases of pemphigus were really cases of severe erythema multiforme and they appear in the literature as cured cases of pemphigus. I do not believe there is such a case.

DR. WHITE: Dr. Mills will speak to us briefly about the eye conditions.

DR. LLOYD MILLS: In discussing dermatology it is perhaps well to get in a plug for the Eye Service. This set of lesions was first described by Dr. Fuchs of Vienna in 1876, although it is usually credited to Stevens and Johnson in this country in 1922. Eye lesions are characteristic of a severe and fulminating pseudo-membranous conjunctivitis in a patient with low resistance. Like other forms of membranous conjunctivitis, they become secondarily infected and perforation of the cornea frequently follows. The most serious consequence other than fatal outcome is perforation of the eye or loss of vision from a complete symblepharon and the formation of corneal membranes, which occur in more than 70 per cent of the reported cases, regardless of age or sex. There is no satisfactory treatment for the eye manifestations during the acute phase of the disease. Ordinarily we give them a bland ointment and wash, such as one per cent sodium citrate, but regardless of what we can do it goes on to destruction of the fornices of the conjunctivae, so they are unable to open or close the lids, and eventually ulceration of the cornea. Possibly this outcome will be bettered by systemic antibiotic treatment.

DR. WHITE: There is one other condition which has been noted in the history of this patient, which may or may not be a red herring. I would like to have Dr. Schatzki point out the findings in the x-rays. The mediastinal involvement was noticed some years ago and radiation and radiotherapy was prescribed and carried out.

DR. RICHARD SCHATZKI: I don't know anything about the case and nothing about the history, Dr. White. This was taken in 1937 (Fig. 6). Did he have his x-ray treatment at that time?

DR. WHITE: Will you briefly review that point?

DR. CRAIGE: The original lymphoma of the hilar nodes was seen in 1933 and treated by 600 R spray radiation of the mediastinum. Those films have been

destroyed. This film was taken at a recurrence four years later and subsequent films show regression of these nodules. So this is the only picture we have which shows the nodular lesions.

DR. SCHATZKI: From the description he had a similar lesion ten years previously.

DR. CRAIGE: Four years previously. He had three round masses that were six by ten centimeters in diameter.

DR. SCHATZKI: From what you can see here this certainly looks very similar to what one sees in sarcoid and in erythema nodosum. Not quite as symmetrical

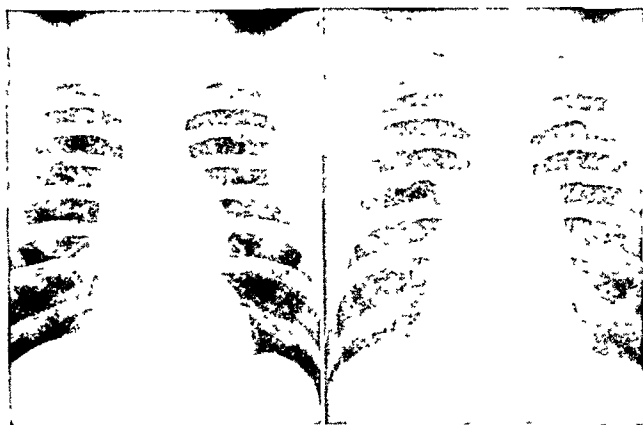


FIGURE 6

August 19, 1937

FIGURE 7

May 27, 1941

as we would like. The inflammation in the left side is more marked than on the right side. He had no skin lesions?

DR. CRAIGE: No, sir.

DR. SCHATZKI: Why did he have the films in 1941 (Fig. 7)?

DR. CRAIGE: That is when he had the previous attack of what he has now, complicated by pneumonia.

DR. SCHATZKI: The acute process is there. And in 1943 his chest looks from a distance practically perfectly normal, but closer you see there is some definite pathology here in the left lower lobe which corresponds to the bronchiectasis which you see. I am at a loss to combine those things for the present.

DR. WHITE: I was going to ask Dr. Swartz if he feels there is any connection between the two.

DR. SWARTZ: I think Dr. Schatzki's statement about the chest findings being consistent with sarcoid or erythema nodosum would simply strengthen the theory that erythema multiforme, mild or severe, falls in the group of diseases which I considered in my discussion.

DR. ARLIE V. BOCK: Do you think he had periarteritis nodosa?

DR. WHITE: I don't think he ever had. There has been no suggestion of nodules.

DR. BOCK: Those nodules, unless you watch for them, can come and go.

DR. WHITE: That has not been under suspicion, but I suppose we might consider it further. I doubt the existence of it. He has gone a long time now.

DR. MAURICE FREMONT-SMITH: What is his trade?

DR. CRAIGE: He is a tile layer. He used to be a truck driver.

DR. W. RICHARDSON: I saw him at the Pulmonary Clinic for several years and suspected that he had sarcoid—at least had sarcoid as far as the chest nodes are concerned. I did not feel he had lymphosarcoma at that time. I was wondering whether the whole thing was sarcoid. I never saw so-called sarcoid do this kind of thing.

## CASE 9

### CARCINOMA OF THE PROSTATE

DR. ROBERT GRIER: Mr. T., No. 479036, is a 67-year-old, former painter, paperhanger and plumber, who first came to this hospital in March 1945. He presented six primary complaints: First, complaints of difficulty in swallowing with occasional regurgitation of food, accompanied by nausea and pain; secondly, he gave a history of 30 pounds weight loss in the past 18 months; thirdly, he had a story of two and one-half years of fleeting pains, which he termed "neuralgia," characterized by pains in various bones and muscles lasting for a day or so and then migrating elsewhere; fourthly, he had a three-year story of increasing dyspnea on exertion, palpitation, and swelling of the ankles; fifthly, he had a one-month story of blurring of his vision, diplopia, and difficulty in recognizing objects at a distance; and sixthly, he had a three-months' story of increasing frequency of micturition, diminution in caliber of the urinary stream, without other urinary symptoms.

On physical examination at that time, he was a well-developed, chronically ill man, who looked pale and wasted, showed the evidence of weight loss, but apparently was in no acute distress.

Examination of the eyes showed a bilateral partial optic atrophy with two diopters of papilloedema, hemorrhages and exudates. He had a perforated nasal septum; his heart and lungs were not remarkable; abdominal examination was negative except for a right indirect inguinal hernia. Examination of the prostate showed it to be enlarged one to two times normal with a single nodule about one centimeter in diameter in the upper part of the left lobe.



Laboratory examination showed a red blood cell count of 2,000,000; hemoglobin 5.7 Gm.; and a normal white blood cell count. Examination of the stool was negative, and the urine was negative; concentrated to 1.026. Blood serological tests were negative; the nonprotein nitrogen was normal.

X-rays taken at the time of admission, including skull, chest, spine and pelvis, showed lesions which were consistent with metastatic disease with bony destruction.

A diagnosis of carcinoma of the prostate was made and he was treated on that basis with a low-calcium diet, 3 mg. of stilbesterol daily, vitamins, and one transfusion. On this regime all symptoms gradually ameliorated. His weight increased from 51 to 62 kilos from the middle of March to the middle of July. He was discharged at that time and followed in the Outpatient Department. He has been living at home, cooking his own meals, walking three or four miles a day. One week ago he papered three rooms in a house, and to all intents and purposes is a perfectly normal individual.

He was readmitted here on the 1st of November for check-up and re-evaluation. At that time the physical findings were essentially as before, with the exception that the prostate was no longer one on which a diagnosis of malignancy could be made; it was firm, slightly enlarged, with one small, soft, nodule in the midline. He has been in excellent health. His red blood cell count is 4.5 million, with the hemoglobin 12 Gm. per 100 cc.

DR. JOSEPH C. AUB: Dr. Robbins, do you want to discuss the x-ray?

DR. LAURENCE L. ROBBINS: The x-ray appearance as seen on the original films is certainly characteristic of the diffuse transplantation type of metastasis that is seen most frequently with carcinoma of the prostate. Practically all of the ribs, pelvic bones, the femur, and lumbar vertebrae are certainly involved. These others seem to be the films taken recently and certainly there is a marked regression in the process. It would be a little difficult to be certain about how much disease goes on within the ribs. There is not much question that there is persistent disease in the pelvic bones and in the spine. In the skull, it is pretty hard to be certain that there is any real change.

DR. AUB: Isn't there some more calcification?

DR. ROBBINS: No.

DR. AUB: While many patients do not respond so favorably, this is a brilliant recovery from what looked like the terminal stages of metastatic carcinoma of the prostate. The bones, riddled with the disease before treatment was started, have improved

remarkably in the ensuing 21 months. The prostate now feels essentially normal except for several possible nodules. His feeling of health has returned to its previous condition, except for his very poor vision. And his only treatment has been 3 mg. of stilbesterol a day.

The laboratory findings are equally interesting. This patient is one of a group being studied metabolically with Dr. Nathanson and Miss Tibbetts.



FIGURE 8  
April 12, 1945



FIGURE 9  
November 6, 1946

There was a dramatic increase in his blood acid phosphatase from 24 to 1,660 (Gutman) units while under observation for two weeks before therapy. There was an equally dramatic fall to 8.6 units in three weeks after stilbesterol was administered, and after four months on medication a normal level was reached. During the subsequent 16 months this enzyme has remained in normal amounts in the blood. The alkaline phosphatase remained high (15–20 Bodansky units) for three months as one would expect in a man who was regenerating bone, and now it has subsided to a normal level. His calcium excretion has remained very low and throughout these months he has stored calcium and excreted very little in his urine. Citrate excretion has also fallen to half its pretreatment level, an interesting finding since the citrate level is highest in both prostate and bone.

So this patient shows well what good results may be obtained with a drug which acts like the female hormones. A similar beneficial result was demonstrated here by Dr. Nathanson in an elderly woman with carcinoma of the breast. These effects, such as demonstrated today, are very interesting; they are the first evidence that tumors can be held in check by the very substance which in other observations have been shown to prepare the substrate on which tumors are developed. The problem is a complicated one. It deserves, and will require, much study before it is well clarified. But here is a promising start, for any substance which will produce such great improvement in a specialized tumor is an important discovery.

DR. JAMES H. MEANS: What do you think his prognosis is?

DR. AUB: I think, as Dr. Robbins says, he still has malignancy. He may have it a long time without its breaking through this barrier. Neoplasms come slowly. They get worse slowly. There are two things in neoplasm. One is the neoplastic cell and the other is the urge to grow. The change to a neoplastic cell, I am sure now, is a slow process, not acute. You don't suddenly have a normal cell and pronto get malignancy. Your cells gradually become malignant, and something like this stops their regeneration. The remaining cells gradually become more malignant.

DR. CHESTER M. JONES: What do you say his prognosis is?

DR. AUB: His prognosis is unfortunate. Most of these patients succumb or break through within two years. There are a few patients who have survived but that have had continuous malignancy for ten years.

DR. MEANS: Another question. If he begins to get worse will you consider orchiectomy? Does that offer anything after he has broken through?

DR. AUB: Not so much. It offers something and the routine of this hospital is to do one or the other, either give stilbesterol or do orchiectomy, saving the other for reserve. At least we have something left.

DR. MAURICE FREMONT-SMITH: Can you do exactly the same thing with natural estrogen as with stilbesterol?

DR. AUB: I think you can do the same thing. Stilbesterol seems a little better.

DR. JONES: Is the dosage of 3 mg. the maximum dosage—anything beyond that probably not very effective? I have seen some cases getting 6 mg.

DR. AUB: Some people have given as much as 50 mg. a day. There doesn't seem to us to be any advantage in giving six over three. If three works you give that. Six gives some nausea.

DR. JONES: And myositis?

DR. AUB: And myositis.

DR. MEANS: Do you mean that stilbesterol is better or just more convenient? It interests me that a totally artificial substance should work better than a natural hormone. Isn't the situation such that the stilbesterol molecule is so formed that it deceives the end organ into believing it is the hormone?

DR. AUB: The trouble with stilbesterol is that it is more of a carcinogenic agent than a natural growing agent. But it is cheap and easy to take.

DR. MEANS: It is a matter of economics and convenience rather than endocrinology.

DR. AUB: I would not want to be dogmatic about it. We sort of depend on it because it is cheap and easy to take.

### Hospitalization of Veterans

The number of veterans hospitalized by the Veterans Administration reached a new all-time high on January 22. VA reported that a total of 119,845 veterans were receiving treatment in VA hospitals and homes and in non-VA hospitals under contract to VA on that date. VA's load of veteran-patients has been increasing steadily. A year ago, 92,276 veterans were hospitalized by VA and six months ago, 99,509.

Of the nearly 120,000 patients under VA care on January 22, a total of 90,470 were in VA hospitals; 15,298, in VA homes, and 14,077, in non-VA hospitals.

While the number of veterans hospitalized has been increasing, the number awaiting hospitalization has

been declining. On January 1, only 22,385 veterans with nonservice-connected disabilities were awaiting VA hospitalization, the smallest number since March, 1946.

The drop was attributed to an increase in the number of beds available in VA hospitals and homes and to a more rapid turn-over of patients because of improved medical treatment.

Veterans with service-connected ailments are given top priority for VA hospitalization, but veterans with nonservice-connected disorders are hospitalized only when beds are available and if they say they cannot afford treatment in other institutions.

# The Treatment of the Migraines

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*Of the common disorders the physician is called upon to treat, migraine is not the least. The authors review a number of therapeutic aids in the management of the attacks.*

One of the most perplexing problems that the practicing physician has to face is the treatment of the migraines. We propose to outline an approach to this problem. It goes without saying that it is of tremendous importance to establish the correct diagnosis. Many works have been written on the etiology and diagnosis of the migraines,<sup>1-5</sup> and the reader is referred to these for more detailed information. The syndrome is characterized by headaches which are associated with emotional disturbances, usually depression, in the majority of cases. The headaches are unilateral at some stage in about four-fifths of instances. Periodicity of attacks is essential to diagnosis. The triad of nausea, vomiting and unilateral headache is almost diagnostic of migraine. The family history is positive in over 70 per cent of cases; indeed the absence of a positive family history casts doubt on the accuracy of the diagnosis. The majority of cases start in the first or second decade and few persist beyond the sixtieth year. There is a high incidence in professional people. Scotomata occur in slightly less than half of the patients but are pathognomonic when present. Photophobia and blurred vision are common but not characteristic. Excessive sweating and vasomotor disturbances are frequent. Less common concomitants include paresthesias, polyuria, confusion, pareses, drowsiness and tinnitus. Because there is no specific treatment available, one must approach the problem from a number of avenues.

It is common information that many women have the attacks with or just before their menstrual period. It is also known that the intensity and frequency of the attacks may decrease or disappear completely during pregnancy and after the menopause. It is thought that this is the result of some disturbance in the hormonal interplay which results in a derangement of water metabolism. Of particular note is the work of Price and von Storck.<sup>6</sup> These workers studied 163 unselected cases and found that only 10 per cent of the women definitely related the menstrual cycle to

the migraine; and in another 22 per cent there was questionable association. Since there is no constancy in the relation of headaches to the menstrual period varying hormones have been used. For example, some individuals recommend the use of 1,000 to 50,000 I.U. a week of estrogenic substances. Because of the known relation of the pituitary gland to the ovarian hormones the gonadotrophic hormones of the anterior pituitary have been used. The judicious use of thyroid extract in women who have a low basal metabolic rate is of real value. The use of female sex hormones in treating males with migraine has its advocates.

Perhaps one of the most widely held conceptions regarding the cause of migraine headaches is that it is on an allergic basis.<sup>7</sup> In evaluating the importance of allergies in the migraines, one must be careful not to let individual and isolated cases influence one. The study of von Storck and Follensby<sup>8</sup> is of considerable importance. They analyzed 862 patients who had been studied by ten different allergists who concluded that 661 cases were definitely allergic. It was said that of this number relief was obtained in from 0 to 100 per cent with the average being 73 per cent; 86 per cent of the 862 patients obtained slight relief, while only some 25 per cent had complete relief. It should be pointed out that these figures are in agreement with the opinion of most conservative allergists. In the study of the allergic factor a number of approaches are available. Skin tests have their proponents, but it is well known that the accuracy of these tests in determining food allergy is by no means that obtained in testing for pollen sensitivity. When the requisite information cannot be obtained in this manner recourse may be had to the use of elimination diets and food diaries. Complete details are discussed elsewhere,<sup>9</sup> but briefly stated perhaps the simplest of the elimination diets is that of Alvarez which is composed of lamb, pear and rice. The patient adheres to this diet for one week and if at the end of this time the headaches still persist, it is unlikely that they are allergic in origin. The food diary consists of enumerating the foods consumed each day, indicating the days upon which the headache occurs. In this man-

ner the physician will be able, by trial and error, to eliminate the offending food.

Perhaps because of the gastro-intestinal disturbances that are frequently associated with an attack of migraine, various digestive organs have been held accountable for this condition; particularly the liver and the gallbladder have been incriminated. It is generally accepted, however, that if there is a disturbance of the gastro-intestinal tract it is coincidental and is not related to the syndrome itself.

The procedure panel illustrates the method of approach used in treating an individual who is suffering from an acute attack of migraine. It has long been known that sedatives are of real value, either alone or preferably combined with ergotamine. The administration orally of ergotamine tartrate in 1 mg. (gr. 1/64) tablets is effective principally as a preventive measure. Usually the patient can anticipate an attack and if he is then given ergotamine tartrate, the episode can frequently be aborted. If the attack has developed, this medication must be given parenterally. The usual dose is 0.5 cc. of 1:2,000 solution. Although this is frequently accompanied by nausea and occasionally by severe vomiting, it has been very effective in our hands in terminating an attack. One must always emphasize to the patient the danger associated with repeated injections of this medication. This is particularly true when a large number of tablets for oral administration are prescribed. The danger of ergot poisoning is a very real one and many individuals have developed gangrene of the extremities from improper administration of this drug. The basis for the gangrene is marked vasoconstriction which manifests itself by tingling and blanching of the extremities. If these symptoms do not occur one is justified in using the drug two or three times a week.

An interesting observation is that of Tillim.<sup>10</sup> While treating morphine addicted individuals by the use of insulin-evoked hypoglycemic reactions, he noted a decrease in the incidence of headaches in individuals who had previously had to resort to morphine for relief. The dose of unmodified insulin required is enough to bring about a fairly marked hypoglycemic reaction and this may vary all the way from 10 to 50 units.

Histamine will at times benefit these individuals. It has been recommended that its use be confined to those individuals who are skin-sensitive to it. One may give it twice a week subcutaneously in increasing doses, starting with 0.1 cc. and administering it over an interval of three or four months. Histamine azo protein (marketed under the name Hapamine) has

definite possibilities. By diazotization, Fell, Rodney and Marshall<sup>11</sup> combined histamine with despeciated horse serum globulin to form an antigen complex in which histamine acted as a hapten. The initial dose of Hapamine is 0.05 cc. and it may be increased at three- to seven-day intervals until 1.5 cc. is given.

We have used, with occasional dramatic success, inhalations of oxygen either as 100 per cent or in combination with carbon dioxide. This form of therapy has its best effect when given early. It is important when using oxygen and oxygen-carbon dioxide combinations that proper masks be used so that optimum concentrations may be attained. Potassium thiocyanate has been advocated by Hines and Eaton.<sup>12</sup> It must be remembered, however, that this is a relatively new form of therapy and by no means free of complications. Various vitamin preparations have been used from time to time, particularly thiamin hydrochloride, but we feel these are of little or no value.

Evidence is accumulating that many of the migraines are to be explained by reference to dysfunction of the cranial arteries. Vasodilatation, accompanied by increase in the amplitude of pulsations, of branches of the external carotid artery (chiefly) results in the development of the attack. When extracranial branches are responsible pressure on them may afford temporary relief. Because of these fundamental vascular disturbances, surgical treatment has been along vascular lines. Various procedures such as bilateral cervical sympathectomy, ligation and resection of the middle meningeal artery, and thoracic ganglionectomy have been advocated. We<sup>13</sup> have had considerable success in individuals who have areas of hyperesthesia by infiltrating these areas with novocaine and eucupin-novocaine mixtures. It is well, however, to point out that these drugs are not without danger.<sup>14</sup> In a study of deaths following the use of these and similar drugs we have concluded that novocaine in excess of 1 per cent strength should not be used, and that it is preferable to add a few drops of epinephrine 1:1,000 solution. This not only renders the area more avascular but also decreases the rate of absorption.

No examination of an individual with migraine is complete without a detailed inquiry into his life and habits because frequently on the basis of information derived from these questions can one offer suggestions which may help decrease the incidence of the headaches. It is held, for example, by Draper<sup>5</sup> that the migraine individual has a peculiar physical substrata, and that these individuals usually have high intelligence and are very conscientious individuals; as Lennox has said, "They experience difficulty in leaving a

task unfinished and in delegating responsibility to others since they are rigid in their attitudes toward their personal relationships."

### PROCEDURE PANEL

- I. Put the patient to bed and loosen garments.
- II. Darken quiet, well ventilated room.
- III. Apply ice cap to area of pain.
- IV. Use oxygen inhalation when feasible. This relieves 40 per cent.
- V. Administer ergotamine tartrate.
  1. Dosage schedule—
 

Intravenous administration	0.25 mg.
Subcutaneous administration	0.5 mg.
Oral administration	1-5 mg.

 Keep dosage to minimum consistent with relief of patient.
  2. Side actions of ergotamine most common after intravenous administration.
    - A. Nausea and vomiting is the rule. After injection, these may be minimized with 0.0006 Gm. atropine.
    - B. "Muscular" cramps may appear along the course of the main arteries of the arms and legs. Massage.
    - C. Temporary paresthesias are frequent.
    - D. Persistent paresthesias contraindicate ergotamine.
  3. Precautions with ergotamine.
    - A. No more than 0.25 mg. intravenously in one dose; no more than two such doses daily.
    - B. No more than 0.5 mg. subcutaneously; no more than two such doses daily.
    - C. No more than 11 mg. orally daily.
    - D. No more than two injections per week.
    - E. No more than six injections per month.
  4. Contraindications to ergotamine.
    - A. Septic states.
    - B. Obliterative vascular disease, especially coronary artery disease.
    - C. Incipient ergotism.
- VI. In protracted cases associated with nausea and vomiting, glucose and saline infusions may be given.
- VII. Narcotics are contraindicated, but sedatives are helpful.

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### BIBLIOGRAPHY

1. Wolff, H. G.: The cerebral circulation, *Physiol. Rev.*, 16:545, 1936.
2. Ray, B. S., and H. G. Wolff: Experimental studies on headache, *Arch. Surg.*, 41:813, 1940.
3. Wolff, H. G.: Headache mechanisms, a summary, In *Pain, Proc. A. Research Nerv. & Ment. Dis.*, 23, 1943.
4. Goltman, A. N.: Unusual cases of migraine with special reference to treatment, *J. Allergy*, 4:51, 1932.
5. Draper, G., C. W. Dupertuis, and J. L. Caughey: *Human Constitution in Clinical Medicine*, New York, Hoeber, 1944.
6. Price, J., and T. F. C. von Storck. Quoted by T. F. C. von Storck: On the treatment of migraine, *Med. Clin. N. A.*, 25:1317, 1941.
7. Vaughan, W. T.: Allergic migraine, *J. A. M. A.*, 88: 1383, 1927.
8. Von Storck, T. F. C., and Edna Follensby. Quoted by T. F. C. von Storck: On the treatment of migraine, *Med. Clin. N. A.*, 25:1317, 1941.
9. Derbes, V. J., and H. T. Engelhardt: *Treatment of Bronchial Asthma*, Philadelphia, Lippincott, 1946.
10. Tillim, S. J.: Migraine headaches relieved by hypoglycemic reaction: report of two cases, *Ann. Int. Med.*, 20:597, 1944.
11. Fell, N., G. Rodney, and D. E. Marshall: Histamine protein complexes: synthesis and immunologic investigations, *J. Immunol.*, 47:237, 1943.
12. Hines, E. A., and L. M. Eaton: Potassium thiocyanate in the treatment of migraine, *Proc. Staff Meet. Mayo Clin.*, 17:254, 1942.
13. Patzer, R., V. J. Derbes, and H. T. Engelhardt: Periarterial infiltration in diagnosis and treatment of migraine, *Arch. Surg.*, 50:296, 1945.
14. Derbes, V. J., and H. T. Engelhardt: Deaths following the use of local anesthetics in transcardiac therapy: a critical evaluation, *J. Lab. & Clin. Med.*, 29:478, 1944.

### Celsus on Epilepsy

That malady which is called comitialis, or the greater, is one of the best known. The man suddenly falls down and foam issues out of his mouth; after an interval he returns to himself, and actually gets up by himself. This kind affects men oftener than women. And usually it persists even until the day of death without danger to life; nevertheless occasionally, whilst still recent, it is fatal to the man. And often if remedies have been ineffectual, in boys the commencement of puberty, in girls of menstruation, has removed it. Now sometimes there is a spasm of the sinews when the man falls down, sometimes there is none. Some try to rouse the patients as is done in the case of those affected by lethargy; which is quite useless, both because not even the lethargic patient is cured by this method, and because, though it may be impossible to awaken him and he may thus die of starvation, the epileptic, on the other hand, returns to himself. If a man falls in a fit without the addition of spasms, certainly he should not be bled; if there are spasms, at any rate he should not be bled unless there are other indications for the bleeding. . . .

—From *De Medicina* book III 23.  
Translation by W. G. Spencer,  
London, Heinemann.

# CASE REPORTS . . .

## Syphilis of the Breast: Chancre and Gumma\*

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At intervals it seems well to call attention to clinical entities which are encountered rarely in any one physician's practice. With the passage of time the memory of such entities may become dimmed, but it is easily renewed by a brief description of the disease in question. For this reason two case reports follow with the purpose of reminding the physician that syphilis may attack the breast.

The case reports illustrate examples of syphilitic lesions which are most likely to be *solitary* and thus offer difficulties of diagnoses. The cutaneous lesions of secondary syphilis obviously involve the skin of the breasts as part of the generalized eruption, thus not offering any diagnostic problem as regards the breast itself. The papules of a secondary papular syphilide may be eroded and moist at the areola, if the patient is a nursing mother, due to the trauma of the suckling. In the woman with pendulous breasts papules in the folds under the breast may become hypertrophic to form condyloma lata, due to moisture, heat, friction and uncleanness. These lesions again are part of wide-spread cutaneous involvement and thus do not suggest disease of the breast itself.

### PRIMARY SYPHILIS OF THE BREAST

The chancre of syphilis usually occurs on or about the genitalia. It is estimated by several authors that 95 per cent of primary lesions are genital in location. This is borne out in our clinic where the incidence of extragenital chancre is 5.6 per cent of 650 and more primary lesions.<sup>1</sup> Most extragenital primary lesions appear on the lips or about the mouth, having been acquired by kissing someone who has the highly infectious mucous patches of secondary syphilis. Similarly through sex play the breast likewise may be the site of a chancre. Though most chancres of the breast occur in women, primary lesions of the male breast have been reported. In past decades, in the day of the "wet nurse," breast chancres were seen more frequently than now due to the nurse being infected

through nursing a child with infectious syphilis of prenatal origin.

### CASE REPORT

The patient was a 60-year-old white woman who was brought into the Syphilis Clinic as a contact of her husband.

**History.** She had noted a pimple on the right breast three weeks before coming to the clinic. At intervals she picked at it, abrading the surface. An ulcer soon developed which became progressively larger exuding a blood-tinged watery discharge. Though the patient was aware of a burning sensation there was no actual pain.

For the week before coming to the clinic she had not felt as well as usual, having lost her appetite and having some headache.

Apparently there had been no sexual intimacy with her husband for a couple of years. About two months before admission to the clinic the patient said she was awakened one night by her husband "either pinching or biting" her right breast. However, there had been no break in the skin.

The patient had been brought into the clinic as a contact of her 64-year-old husband who had been admitted about six weeks before with lesions of the lips. He was shown to have two labial chancres, one on the upper and one on the lower lip. (The disease was acquired by kissing a 13-year-old neighbor girl who had had a "rash.") The patient and her husband had not slept together since the diagnosis was established in his case. She was unaware of the husband's diagnosis.

**Examination.** The only finding of interest was the lesion on the right breast. Just below the areola was a firm, though not markedly indurated ulcer about 1 cm. in diameter. It was covered by a crust and was surrounded by a zone of redness. Removal of the crust left a clean ulcer exuding serosanguineous fluid. This contained *T. pallidum* upon darkfield examination. There was no axillary lymphadenopathy. Blood Wassermann and Kahn tests were positive. (These had been negative one year before while the

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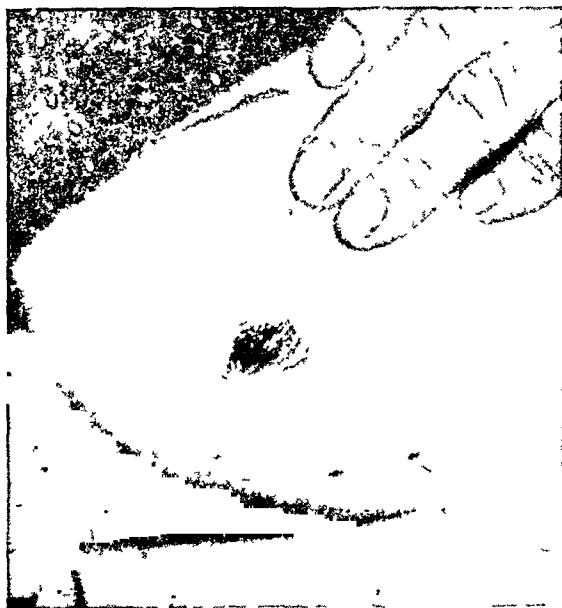


FIGURE 1

patient had been on the gynecology ward.) The diagnosis was chancre of the breast. (Fig. 1.)

Response to antisyphilitic treatment was prompt.

**Comment.** The above example of chancre of the breast was chosen because it appeared in a woman 60 years of age, a circumstance which might lead a physician to discard the thought of syphilis if it had entered his mind in the first place. One would not anticipate such a lesion in an age beyond that of sexual activity, though it was unquestionably transmitted from the husband's lips. We had the advantage of knowing that the 64-year-old husband had chancres of the lip acquired by kissing a young girl. In the absence of this knowledge any physician well might be excused for missing the diagnosis of a primary lesion of the breast in a 60-year-old woman.

**Discussion.** Tobias<sup>2</sup> quotes a statement made by Fournier many years ago, "To diagnose an extragenital chancre is simple, to keep it in mind is difficult."

All too often the extragenital chancre is not diagnosed because of two facts. The first may be the unusual location of the ulcer, thus there is no connection in the physician's mind with exposure to syphilis because of the apparent nonsexual origin of the lesion. The second is the atypical nature of the lesion.

Though most physicians consider the diagnosis of syphilis in ulcers of the mouth or lips, other extragenital chancres may not be recognized as such because of their unusual sites and an irrelevant history. The patient may be quite honest in his history since he, or more often she, relates it in no way to possible exposure to syphilis.

The belief is fixed too firmly in the minds of physicians that all chancres have the so-called "hunterian" characteristics when in their full-blown state. The "typical" chancre appears first as a red papule with little induration. Next the surface of the papule becomes eroded and increases in size to the characteristic primary lesion varying from 0.5 to 2 cm. in diameter. When this stage is reached it commonly presents a nontender clean ulcer, covered by a crust of dried serous exudate. The borders of the ulcer are even and rolled and the base is of cartilagenous hardness. The lesion is often described as a "button in the skin." However, the *extragenital* chancre is more likely to be "atypical." Thus the hardness may be lacking, there may be more tenderness, and there may be a greater tendency to bleed. (It is true that these atypical features are encountered more often in chancres of the lips.) The characteristics of the chancre may be further modified by local treatment with irritants and by superimposed secondary infection. Therefore commonly the regional lymph nodes are more prominent than the usual "sentinel node" of the genital chancre.

Fournier's statement was made before the *Treponema pallidum* was known. However, the diagnosis of chancre usually is simple if suspected. The demonstration of the organism by darkfield examination establishes the diagnosis as in the above case. However, it must be recognized that the application of ointments and other medicaments may sterilize the surface of the ulcer temporarily with a resultant darkfield examination. The application of hot saline packs for some hours after removing the crust and medicaments will facilitate the demonstration of the *T. pallidum*.

The diagnosis of chancre of the breast is not likely to involve a differentiation from serious chronic disease. The rather acute onset and self-limited course in a matter of a few weeks at most is likely to influence the physician to think of some nonspecific localized skin infection. If, however, the nipple itself were involved the question of Paget's disease might be considered in diagnosis. This, however, would not be likely to reach the degree of ulceration occurring in a chancre within such a brief time.

### GUMMA OF THE BREAST

Late benign or tertiary lesions of the breast are much rarer than are primary sores. It is unquestionably true that gummatous mastitis will become still more rare. With a greater percentage of syphilitic patients receiving treatment and with the use of more adequate therapy, tertiary lesions, which used to be

common as in the case of skin, bones, etc., are becoming fewer.

The last report on gumma of the breast appeared in 1940 being recorded as the 52nd case in the literature.<sup>8</sup> It thus seems clear that this lesion represents a rare form of gummatous syphilis. The case to be reported here is the only one occurring in 610 cases of late benign syphilis which have been registered in the Syphilis Clinic of Vanderbilt University Hospital in a 20-year period. This is an incidence of 0.16 per cent.

#### CASE REPORT

The patient was a 30-year-old negress admitted to the Surgery Clinic because of a "lump in the breast."

**History.** The onset occurred two months before admission when the patient first noted the lump while bathing. At that time it was described as being about 1½ cm. in diameter. There was no associated pain. The patient said that at first the mass was soft but that it had become hard.

**Examination.** This was negative except for the findings related to the right breast. The description of the lesion on the first admission was as follows: A hard mass about 4 cm. in diameter was present in the upper portion of the right breast. It was attached to the skin with marked dimpling of the skin over the lesion especially as the patient lay on the left side. The lateral pectoral nodes were palpable on the right.

**Course.** She was to be admitted to the surgical ward for operation several days later. (The blood Wassermann and Kahn tests were positive on the first



FIGURE 3

visit.) The patient did not keep her appointment, however, and next returned two months after the first visit. About five weeks after the first visit to the Surgery Clinic, two "pimples" appeared over the tumor in the breast. They ruptured to drain a watery fluid. Ulceration developed becoming progressively larger.

**Examination.** on this second visit to the Surgery Clinic revealed an ulcer about 4.5 cm. in diameter. The edges were rolled, the floor was covered by a crust. Induration extended about 1 cm. beyond the borders of the ulcer. There was one moderately large sized lymph node palpable in the right axilla. (Fig. 2.)

It now was felt by the surgeon, Dr. Ralph M. Larsen, that the ulcer might well be of gummatous origin, and accordingly the patient was seen by us in the Syphilis Clinic. Here the history threw no light upon the duration of her syphilitic infection. (The husband was found to have positive blood tests.) The examination provided no evidence of other syphilitic lesions. Blood Wassermann and Kahn tests were repeatedly positive.

Antisyphilitic treatment was begun with bismuth subsalicylate in oil 0.13 Gm. weekly. By the third week the ulcer was smaller and cleaner, and was filling with granulating tissue. The lesion was healed after seven injections of bismuth. (Subsequent treatment consisted of alternating courses of arsenic and bismuth during the following two years.) The resulting scar at this time is shown in Figure 3.

**Comment.** The clinical diagnosis upon the pa-

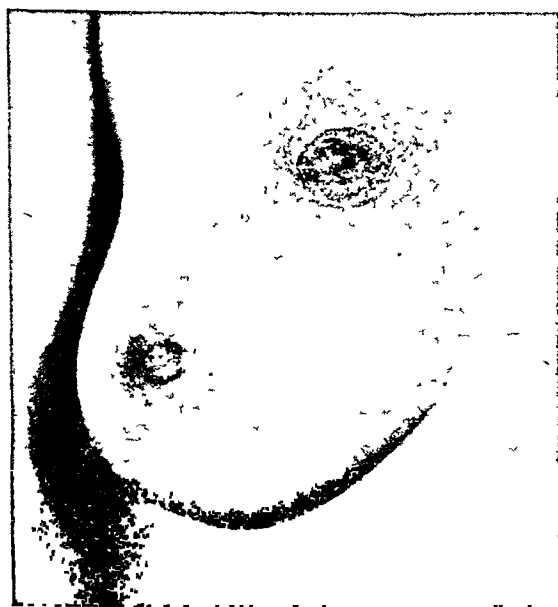


FIGURE 2



tient's first visit to the Surgery Clinic was that of a tumor necessitating operation. This was the logical advice to give in view of a tumor found accidentally two months previously, increasing in size and being accompanied by dimpling of the skin. Only the patient's lapse from the clinic for two months with breaking down of the lesion led to the correct interpretation of its significance as related to the positive blood tests.

**Discussion.** Gummatous mastitis offers as its great problem the differentiation from carcinoma. In most instances the diagnosis is made by the pathologist after mastectomy. (The pathologist may be unable to differentiate as between syphilis and tuberculosis, and positive blood tests for syphilis may be a determining factor.) This is not offered as a criticism since the overwhelming majority of lesions presenting the clinical picture as encountered in gumma of the breast would and should be interpreted as probable carcinoma, even though blood tests for syphilis are positive. It is unquestionably true that many more instances of carcinoma and benign noninflammatory tumors of the breast are encountered in the presence of latent syphilis (positive blood tests for syphilis without clinical evidence of disease) than examples of gummatous mastitis. The rarity of gumma as compared to carcinoma is attested to by Adair, quoted by Stokes,<sup>4</sup> who found one gumma among 1,674 cancers of the breast. The enlarging tumor, the accompanying enlargement of pectoral or axillary lymph nodes and the dimpling of, or "orange-peel" appearance of the skin overlying the tumor in both conditions may make differentiation without the aid of the microscope impossible. Therefore it is clear why the reported instances of gumma of the breast in recent decades have been recognized only after mastectomy. The recorded cases in which operation was not done

and in which time and treatment revealed the true nature of the disease appear in the literature of the last century and the earlier years of the twentieth century. If ulceration occurs it will appear much sooner in the gumma than in carcinoma.

The differentiation from tuberculous mastitis is also difficult, although this is more likely to be accompanied by sinus formation rather than frank ulceration as in gumma. (Roentgenologic examination would assist in making the diagnosis of tuberculosis of pleura or rib or of syphilitic osteitis accompanied by sinus tracts through the breast.) Rarely do granulomas occur as the result of fungus infection. Actinomycosis with sinus formation would most likely have its origin in the lung and the x-ray of the chest as well as the characteristic sulphur granules in the discharge would aid in diagnosis.

### SUMMARY

With the aid of illustrative cases, the surgeon has been reminded that syphilis may be encountered as a cause of breast lesions.

Chancre of the breast may be met with occasionally as an example of an extragenital primary lesion.

Gumma of the breast is so rare that except for unusual circumstances it will be diagnosed only by the pathologist after mastectomy.

### BIBLIOGRAPHY

1. Kampmeier, R. H.: *Essentials of Syphilology*, Philadelphia, Lippincott, 1943.
2. Tobias, N.: Extragenital chancres: a clinical study, *Am. J. Syph., Gonorr., & Ven. Dis.*, 20:266 (May) 1936.
3. Braunstein, A. L., and R. D. Woolsey: Gummatous mastitis, *Am. J. Syph., Gonorr., & Ven. Dis.*, 24:43 (Jan.) 1940.
4. Stokes, J. H.: *Modern Clinical Syphilology*, Philadelphia, Saunders, 1926.

### Answer to WHAT'S YOUR DIAGNOSIS? in December Issue

The report of the pathologist on the case abstracted in the December number is as follows:

#### Disseminated lupus erythematosus.

Seventy-five per cent of those submitting a diagnostic solution of this problem were correct. Among the remaining diagnoses were acute leukemia, rheumatic fever, Hodgkin's disease, acute nephritis, rheumatic heart disease and streptococcus viridans septicemia. The high percentage of those with the correct diagnosis is of interest. While gratifying, it is apparent that the high percentage may have been in part due to the fact that only those who felt quite sure of the correctness of their answers sent them to the editor. It is hoped that an increasing number will "take a chance."

# WHAT'S YOUR DIAGNOSIS?

A 39-year-old white housewife was admitted to the Medical Service complaining of weakness, shortness of breath and swelling of her abdomen.

The history which was given by the patient was apparently rather vague and the details as recorded by different examiners varied considerably. The patient dated the onset of her illness to a few days after her pregnancy, three months previously. This was her fourth normal pregnancy (she had had several abortions) and she delivered spontaneously a viable child at term. The pregnancy had apparently proceeded normally. From time to time there had been slight ankle edema. During the seventh month her physician examined her and told her that her urine and blood pressure were normal. Following delivery she bled profusely until her physician introduced a pack. Several days later she noticed swelling of her ankles and complained of general weakness. During the following five to six weeks she had rather profuse night sweats and occasional episodes of "fluttering" in her chest at which time she was forced to sit up to catch her breath. There were no chills, hemoptysis or known fever. During this time she was alternately up and confined to bed. When up on her feet swelling of her ankles became pronounced. She apparently began to feel better until about six weeks before admission when she rather suddenly developed dyspnea and mild orthopnea. These symptoms gradually increased and she developed a mild but persistent cough. Twelve days before she was seen in the hospital the dyspnea and orthopnea increased markedly and she rather suddenly developed massive edema of her legs and her abdomen began to swell. There were bouts of cough which induced vomiting. Orthopnea became so severe that she had to sleep sitting in a chair. Her physician administered digitalis without any apparent effect. Four days before admission she had a violent spell of coughing and raised an estimated cupful of frothy material streaked with bright blood. The cough persisted and she began taking quantities of salt in an effort to obtain relief. There were no chills or feverishness.

The past history was of interest mainly because of her habits of self-medication. She apparently took many medicines for minor complaints including headache and arthralgias. For 20 years she was accustomed to taking soda postprandially to relieve fullness, and also consumed a ten-cent bottle of turpentine almost daily. She had bouts of diarrhea from time to time for which she took paregoric. However, her general health was apparently good.

On admission to the hospital, physical examination revealed a pale, dyspneic, orthopneic woman who showed marked edema of legs, back, abdominal wall and to a lesser extent the forearms and hands. There was no obvious cyanosis. T. 99.2°, P. 120, R. 40, B.P. 130/80. The ocular fundi were normal. The neck veins were not visibly distended. There was dullness to percussion and diminished breath sounds at both lung bases. Many moist râles were heard at the level of the angle of the scapulae bilaterally. The heart was slightly enlarged to percussion to both the right and the left. The P.M.I. was neither visible nor palpable. The rate was rapid, the rhythm regular. A gallop rhythm was described. The sounds were distant but of normal quality. There were no murmurs. The radial arteries were not thickened. The abdomen was distended and there were obvious signs of fluid. No viscera were palpable and there was no tenderness. Pelvic examination was not done. The tendon reflexes were hypoactive.

The patient was put on the usual cardiac regime and was given digitalis and mercurial diuretics. Despite a fairly good diuresis and some improvement in her edema, the dyspnea and orthopnea persisted and it was necessary to use an oxygen tent. Because of the findings of a leukocytosis and x-ray evidence of pneumonitis, she was given sulfadiazine by mouth. Her temperature ranged from 99° to 100°. The tachycardia increased to 130 and her respiratory rate ranged from 40 to 50. Course râles and rhonchi appeared throughout both lung fields. She died suddenly on the third hospital day.

## LABORATORY DATA

Erythrocyte Count: 4,300,000; 3,600,000.

Hemoglobin: 7.0 Gm.; 6.6 Gm.

Hematocrit: 22.

Leukocyte Count: 31,600; 38,000; 50,000.

Differential: Stabs 2%; Segs. 95%; Lym. 2%; Mono. 1%. (Essentially the same on two occasions.)

Urine: Sp. Gr. 1.012, Alb. 0, sugar 0, bile 0. Few WBC, no RBC or casts.

Serum NPN: 36.

Serum Proteins: Alb. 2.7, Glob. 2.6, total 5.3.

Sputum: Thin, fluid, light brown. Numerous gram-positive diplococci on smear.

Chest Plate: (Portable) Diaphragm high on both sides. Bilateral pleural effusion. Marked passive congestion in bases. Pneumonic area in left base.

Electrocardiogram: Rate 125, P-R 0.12, QRS 0.08; S1 and 2 deep; T1, 2, and 4, flat; Q4 small; ST4 slightly elevated.

# BOOK REVIEWS . . .

**THE NERVOUS CHILD.** By Hector Charles Cameron.  
Fifth edition, New York, Oxford University Press,  
1946. \$3.00.

The author states in his preface to this edition that he resisted the "temptation to rewrite the little book completely." The reason for this resistance is not apparent. It would seem that it might have been better to allow it to die with the fourth edition. The author's discussions of the relationship of parents to their children are at times excellent, but his discussions of medical matters are inexact and largely outdated. All in all there is little to recommend the book.

J. C. PETERSON, M.D.

**HOW TO LIVE.** By Irving Fisher, LL.D., and Haven Emerson, M.D. Twenty-first edition. 354 pages.  
New York, Funk & Wagnalls, 1946. \$2.50.

This has been a popular health book for the layman for many years, as is attested by the numerous editions printed during the past three decades. It probably can be safely recommended by the physician for reading by his patients.

As is commonly the case with books of this general nature, the scientifically trained medical man is prone to become impatient with the methods used in the presentation of information. Thus this reviewer finds fault with the crusading attitude taken by the authors in discussing what they call the "poisons," namely, caffeine and theobromine-containing beverages, tobacco and alcohol. Though the authors attempt to prove their contentions with quotations from the medical literature, these are, on the whole, only generalizations. With respect to alcoholism the authors have failed to remain abreast of modern medical thinking. They describe alcoholism as a cause of mental disease rather than as a symptom of mental disease.

In the opinion of the reviewer the nutritional and dietary sections are not properly presented. Not enough is said about meat in the diet; in fact it is put in a dubious light. The reader leaves the book with the impression that emphasis has been put on vegetarianism, whether by the authors' design cannot be determined. Thorough mastication of food is urged and ill-effects are ascribed to the "bolting" of food, scientific findings to the contrary notwithstanding. Statements such as "mustard, pepper, ginger, hot spices and sauces of all kinds . . . create nerve tensions that require sedation" are without scientific foundation.

The overemphasis on foci of infection harks back to the time of a couple of decades ago. Surely pyorrhea is not a common source of systemic disease, nor can one often ascribe remote disease to teeth, tonsils, sinuses, gallbladder, appendix or intestine. It is stated that "so-called rheumatism, arthritis, neuritis, sciatica, neuralgia, lumbago and other ailments of this nature are frequently found to be related to some form of focal infection. . . . In most cases prompt relief follows removal of the source of the local or focal infection." If this were only true!

In addition to discussion of foods, "poisons" and infection, there are sections devoted to the skin, clothing, work, exercise, and mental health. The authors recognize that the semitechnical presentation is liable to invite criticism on the score of accuracy but believe it necessary to reach the layman. But, such a presentation may also leave false impressions with such readers.

R. H. K.

**NURSING CARE IN CHRONIC DISEASES.** By Edith L. Marsh, R.N. 237 pages with 28 illustrations.  
Philadelphia, Lippincott, 1946. \$3.00.

The author attempts to analyze the presently expanding problem of care for the aged. Everyone is aware of the far-reaching medical and socio-economic phases of an aging population. In this book a brief survey is made of this problem and what is or is not available for the institutional care of the aged and chronically ill.

The major portion of the book is given over to the discussion of the problems of care in the patients suffering from carcinoma, heart disease, arthritis, multiple sclerosis, various types of paralyses and other neurologic disorders. Nutrition, physical therapy and occupational therapy are touched upon.

In the reviewer's opinion a weakness of this book is the lack of emphasis on broad principles of care and the tendency to enumerate details at too great length. The reviewer also questions the need for the discussion and description of details that fall into the province of the physician. As an example, may be cited the presentation of treatment of uterine carcinoma by surgery, x-ray and radium therapy. One might also question the value of including case reports, as the several of multiple sclerosis.

To the nurse or attendant caring for the aged and chronically ill, this book can offer suggestions and assistance.

R. H. K.

# The Influence of Complications on the Treatment of Peptic Ulcer\*

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*Recurrences of peptic ulcer may be reduced if the medical management of the disease is such as to forestall or correct the common complications. The author discusses these complications and shows how they may be handled.*

Ordinarily a relatively early peptic ulcer heals without difficulty, the symptoms subside promptly, healing is complete within a few weeks. However, with the great tendency to recurrence and often with increasing difficulties in controlling symptoms as well as influencing healing, we should look more critically into the problem to learn what factors either cause or contribute to chronicity.

Complications of peptic ulcer make up a very intimate part of the life cycle of this lesion; therefore to discuss the clinical picture is to include at least the major complications. A thorough understanding of these various complicating influences makes for a better appreciation of the difficulties in healing the ulcer, and also explains the chronicity and the great tendency to recurrences. Until specific measures are developed to cure the ulcer we will be forced to take full advantage of our present knowledge of factors contributing to recurrences. The disease peptic ulcer continues to be a medical problem, until the major complicating problems appear, when surgical treatment is recommended.

The acid pepsin theory of ulcer origin is the concept held by most physiologists and clinicians at the present time. Many contributing factors are taken into consideration, however, and dealt with in general therapy. In general the treatment is directed toward lowering the gastric juice by antacids, rest and proper diet and hygiene.

Recognition of certain disorders which complicate an otherwise simple ulcer problem is essential. These complications are:

1. Pyloric obstruction
2. Continuous secretion or hypersecretion
3. Hemorrhage

4. Postoperative ulcers and gastric dysfunctions
5. Alkalosis
6. Perforation
7. Psychogenic disturbances
8. Systemic disorders
  - a. Foci of infection
  - b. Malnutrition
  - c. Allergies
  - d. Renal damage
  - e. Constipation
  - f. Psychoneurosis

## PYLORIC OBSTRUCTION

Obstruction from edema with spasm and cicatricial stenosis must be differentiated. Obstruction in general is recognized by the presence of night distress, vomiting of food and excessive gastric secretion, aspiration of excess secretion at midnight or in the morning before breakfast, delayed emptying of the stomach (observed in the roentgenographic study), visible hyperperistalsis, moving sounds demonstrated over the large partially filled stomach, and finally emaciation and dehydration.

Of the two conditions, obstruction from edema with spasm is by far the more common. Painful night-and-day distress and excessive gastric secretion with bouts of vomiting occurring in cycles every two to six months suggests this type of obstruction.

Vomiting of food eaten the day before, the presence of visible peristaltic waves and an associated distress characterized by fullness and not pain is highly suggestive of obstruction from scar-tissue narrowing. This latter group makes up about 20 per cent of all the patients with clinical obstruction. It is extremely important to make this differentiation because a large majority of this latter group will be candidates for some type of surgical intervention. Recognizing this complication serves to direct attention to these perverted physiologic functions in a way to treat the patient successfully.

The management of ulcer with obstruction consists of neutralization of acidity and aspiration of the stomach. Antacids are given hourly throughout the 24 hours for a period of three to six days to combat

\* From the Department of Medicine, Northwestern University Medical School, and the Evanston Hospital. Read before the Kansas Medical Society, Wichita, Kansas, April 24, 1916.

the excessive secretions so commonly present in obstruction. Aspiration of the stomach is done at 10 P.M., midnight and 7 A.M. before breakfast. Within a few days the amount aspirated usually shows a marked decrease and the midnight and morning aspiration may be discontinued. A decrease of the amount of gastric content aspirated permits an estimation of the decrease of obstruction. If the secretion decreases promptly and the stomach empties as shown by test meals and x-ray studies, it may be assumed that the obstruction is largely from spasm and edema and the subsequent care is that usually recommended for ulcer. When excessive secretions continue to be found or a large amount of food is recovered after a regime of several weeks, scar-tissue narrowing of high grade is present. All efforts should then be directed toward proper preparation for surgical intervention.

Surprisingly successful medical management is often possible in the case of an aged patient with obstruction who is, according to all reasonable rules, a poor surgical risk. Excessive continued or hypersecretion should be suspected in every case of pyloric obstruction. Its presence greatly hinders the healing of the ulcer, aggravates the spasm by continued irritation of the ulcer and increases the pyloric obstruction. It should be suspected when night distress is acute and difficult to control and may be considered proved when an excessive gastric secretion is removed at midnight or from the fasting stomach.

### HEMORRHAGE

Bleeding seldom occurs from a peptic ulcer while the patient is on a careful regime. Nevertheless it has been reported in as high as 20 per cent of gastric ulcers and 35 per cent of duodenal ulcers. Although these figures seem too high they do serve to emphasize the importance of complication in the general consideration of the ulcer problem.

In the absence of previous ulcer symptoms, tarry stools may be the first sign of hemorrhage. Stool on the finger after rectal examination should be observed and tested with benzidine. This test may reveal the cause of previously unexplained anemia and weakness. Even more often than is usually suspected, moderate bleeding causes these symptoms. When severe hemorrhage occurs, vomiting of "coffee grounds" and even bright blood is the rule. Stools are then black, tarry and contain partially digested dark blood; with excessive bleeding, red blood may be observed. The patient is nauseated, vomits, has a desire to evacuate the bowel and may faint. Large quantities of blood may be lost. It is often difficult to differentiate

the bleeding of gastric or duodenal ulcer from ruptured esophageal varices in cirrhosis of the liver, Banti's syndrome, carcinoma of the stomach, benign tumor or purpura. Treatment of the hemorrhage is of prime importance regardless of the cause. As a rule, there is no need for alarm in the most severe bleeding. Uncontrolled hemorrhage is likely to occur where the person is above 50, has evidences of arteriosclerosis, or when a penetrating ulcer has eroded a large vessel in the pancreas. The young patient who has had three or four hemorrhages should be given the advantage of a conservative medical regime following the principle of Sippy or some modification as recommended by Muehlengracht. The patient should be placed in bed, given a hypodermic injection of  $\frac{1}{4}$  gr. (0.016 Gm.) morphine and offered neither food nor fluid by mouth until nausea has subsided. After the nausea and vomiting has ceased, the patient is given a powder consisting of 20 gr. (1.2 Gm.) calcium carbonate and 5-gr. (0.3 Gm.) of heavy magnesium oxide every hour for a period of 24 hours. Or, if there is reason to suspect some kidney damage, 2 drams (8 cc.) every hour of an aluminum gel preparation should be used. Beginning the second 24 hours, 2 oz. of whole milk is given on the hour. This regime should be continued for two or three days, depending upon the time when it is assumed hemorrhage has terminated. From that time on any regular ulcer management is followed, with frequent bland foods given every two to three hours during the day. Transfusion may be advised if the red blood cell count has dropped below two million. To control the hemorrhage but primarily for general support of the patient, whole blood may be repeated every day or two as the conditions indicate. Large transfusions are seldom recommended in the first 24 hours, although the patient and donors should be properly typed with a view to an emergency. If the prothrombin and bleeding times are not normal, vitamin K should be administered at once. Loss of blood volume and shock may be controlled with plasma, and normal saline solution given slowly intravenously.

### POSTOPERATIVE ULCERS AND GASTRIC DYSFUNCTIONS

Many of the surgical procedures exact such penalties as marginal or jejunal ulcers, dumping stomach and other disordered functions, as well as anemia, achlorhydria and malnutrition.

The indications for surgery of peptic ulcers as implied in the above discussion may be briefly stated: acute perforation, late or chronic perforations, perigastric abscess, recurrent ulcer of slow perforation

type, obstruction at the outlet from scar-tissue formation, recurrence of massive hemorrhage after well-controlled medical management has failed, and finally, where carcinoma is suspected or diagnosis is not certain.

This is not the place for extended discussion on the types of surgical procedures but the internist is constantly placed in a position of being forced to review critically the end results of surgery. Furthermore his council is regularly being sought by the patient and family as to the type of surgery and the expected results.

Surgery of the stomach and duodenum is not without considerable hazard even in the most skillful hands. It is obvious that any surgeon assuming the responsibility of an operation should be prepared for whatever is indicated; also he should realize that the more extensive the procedure becomes, the greater the increase in mortality as well as morbidity. In the older age group with long-standing trouble, gastroenterostomy should be done for obstructive lesions at the pylorus. Excision must be done in gastric ulcers. Extensive subtotal gastrectomy should be left to experienced surgeons; it is hoped that a less radical and more rational procedure will be found to replace this one. Vagotomy presents a most intriguing prospect. Insufficient time has elapsed to justify an opinion on it, but the results thus far reported are excellent. Vagotomy is further indicated as a means of controlling the gastric secretion without sacrificing the stomach.

### ALKALOSIS

A possible conflict in the management of peptic ulcers occurs from excessive alkali intake and abnormal loss of gastric juice. It is seen very seldom on a well-supervised service. Except in the presence of renal damage or following gastric hemorrhage, it is scarcely ever observed in young persons. When alkalosis does occur, the usual antacids such as calcium carbonate and sodium bicarbonate must be administered with great caution; usually alumina gels, tribasic calcium or magnesium phosphate should be substituted.

Excessive loss of gastric secretion from vomiting or aspiration occurring in conjunction with pyloric obstruction, especially in association with continuous secretion, is the most common cause of alkalosis. Such loss disturbs electrolyte balance, which increases trauma to renal tissue. When this is already damaged a serious vicious cycle results.

Alkalosis should be suspected when distaste for food, nausea and vomiting, weakness and headache appear. Blood chemistry studies may then reveal an

increase in the serum  $\text{CO}_2$ , a decrease in the chlorides and an increase in the urea and nonprotein nitrogen. The physician should be alert to this complication and recognize it before irreversible damage has occurred.

When a diagnosis of alkalosis has been established, all alkali must be discontinued. If the patient is not vomiting, 5 Gm. of sodium chloride in divided doses is given in 24 hours. Since, however, alkalosis so frequently occurs in pyloric obstruction with continued secretion, parenteral normal saline solution is given to combat chloride depletion and dehydration. In addition, 10 per cent glucose in saline solution, amino acids, plasma or whole blood may be given. Acid forming salts are never recommended.

### PERFORATION

Acute perforation of an ulcer of the stomach or duodenum is a complication demanding prompt recognition, and usually immediate operative treatment. Diagnosis is aided by history of known or suspected peptic ulcer, combined with the physical findings of board-like rigidity of the abdomen, sudden onset of pain and shock. It may easily be confused with renal colic, acute intestinal obstruction, acute appendicitis, acute pancreatitis, acute cholecystitis, mesentery occlusion, ruptured ectopic pregnancy and coronary thrombosis.

Subacute and chronic perforations present symptoms less severe than those of acute perforations. They may not require immediate operation, but frequently add much disorder in disturbing the physiologic function of the stomach by formation of adhesions, abscess or involvement of the pancreas which warrant later operation. Such a perforation is one of the causes of chronic ulcer which fails to respond to careful medical ulcer management.

### PSYCHOGENIC DISTURBANCES

It is generally accepted that unusual or persistent emotional upsets contribute to the recurrences of peptic ulcer activity, perhaps to the actual precipitation. It is difficult to prove more than casual relationship between emotional upsets and ulcer activity, but experience supports a correlary that successful management of the ulcer patient requires an understanding and an appreciation of his social status, security, fears and uncertainties. The pertinent questions are: what are his major desires, anxieties and resentments? No treatment of ulcer will accomplish more than control of the present and temporary attack. What we are particularly desirous of doing is preventing recur-

rences, and this can be greatly influenced, among other things, by directing the attention of the patient to the need of good mental hygiene. Explain to him the relationship between emotional upsets and gastric function, the need of rest and tranquility. All this must be especially emphasized when the evidence seems to point to a neurogenic factor as the primary causative agent. The necessity for re-education and revision of the mode of living becomes quite apparent to the experienced physician and to the alert and conscientious patient.

It seems fair and proper to discuss psychoneurosis as a complicating factor in the problem of peptic ulcer when one recognizes the frequency with which the patient is found to be distraught, apprehensive and discouraged over these recurrences and over his seeming inability to control his ulcer problem. We speak of reassurance as a needful phase of therapy but forget that the state of mental instability which calls for it is not necessarily the cause of ulcer but the result of it. The psychotherapeutic approach should be direct and on a clinical, psychologic basis. At our present state of understanding it is difficult to estimate the role of psychoanalysis, although undoubtedly there will be a place for it with certain patients. One suspects that this approach will be largely preventive.

### SYSTEMIC DISORDERS

With the uncertainty of the prime etiologic factors in ulcer, the role of focal infections assumes importance. The treatment of these conditions is briefly that of removing teeth or tonsils and draining sinuses wherever it can be proved that infection of any of these exists. This is the general management indicated in the presence of any general illness. It is always difficult to predict that a given focal infection has been a primary causative agent in the formation of ulcer.

Complications resulting from operative procedures are concerned with improper or malfunctioning stoma and intestines, marginal ulcers, anemia and recurrences of primary ulcers.

Malnutrition usually does not result from insufficient caloric intake but from the restriction of proper, balanced foods and a corresponding deficiency in vitamins and minerals. Each diet should be carefully scrutinized to evaluate the vitamin content and if found inadequate should be increased by particular attention to vitamin C and the B complex. A deficiency in these two factors undoubtedly contributes

to frequency of hemorrhage, delay in healing and disturbance in the secretory and motor function of both the stomach and intestine. In the early management of peptic ulcer, 500 mg. of sodium ascorbate is given parenterally daily and the B complex intramuscularly or orally as compressed yeast. This procedure is particularly recommended following gastric hemorrhage or in the presence of the nutritional disturbance following pyloric obstruction. A deficient nutritional state should be thought of as a complication, because a long continued inadequate diet may have been thoughtlessly permitted by the physician and followed by the patient.

Constipation is seldom a complication of peptic ulcer but a result of a poorly balanced diet. When the food intake is limited or the particular medication is constipating, magnesium oxide should be given. Constipation or excessive irritation from laxatives may cause abdominal distress which is frequently confused with the original ulcer distress.

Food allergies are often observed in the ulcer patient and yet the symptoms resulting from this source of irritation are sometimes ascribed as a primary ulcer symptom. This may well be expected since the foods which are common offenders in allergic individuals, milk, eggs, wheat cereals, and the like, are the common foods of ulcer diet. This should not be over-emphasized, but on the other hand should not be overlooked. When, in a patient who has been on ulcer management for a long time, irritation simulating ulcer distress persists and is unresponsive to the usual management, an allergic reaction may be suspected. The removal of milk and/or eggs from the diet may give prompt relief.

### SUMMARY

Chronicity of peptic ulcer implies recurrences. Recurrences may be greatly reduced in the general, medical management by careful consideration of the above-noted complications. Except in acute perforation, surgery should not be advised unless a rational, medical regime has first been intelligently followed for an adequate time.

A rational regime presupposes an understanding of the prime factors which retard healing. These factors are: acid pepsin digestion, pyloric obstruction with gastric retention with hypersecretion, nutritional disorders and psychogenic disturbances.

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# Amino Acids in Nephrosis\*

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*In this consideration of the nephrosis of childhood, the role of amino acids is emphasized. Their use as a therapeutic agent is discussed.*

Nephrosis has been defined in many different ways. For the present purpose, it will be defined as that condition occurring mainly in children under three years of age and characterized under three main categories of pathology, biochemistry, and the clinical syndrome. Pathologically, there is always a swelling of the lining cells of the renal convoluted tubules with some vacuolization, and sometimes changes in the glomeruli, in the liver, and in other tissues. Biochemically, there are in the main two comprehensive, and several individual, analytical findings. The first comprehensive finding is a negative nitrogen balance; the second, either a low positive or a negative calcium balance. In consequence of this inability of the body to prevent output exceeding intake, there are changes in the concentration of some of the components of blood. These changes pertain to serum, and result in subnormal concentrations of albumin, calcium, and amino acids. Superimposed, though not necessarily related in origin, there are supernormal concentrations of lipids and cholesterol. Incidentally, the ratio of cholesterol esters to free cholesterol is unchanged from that in average normal individuals. The deficiency of protein in the body is aggravated by a proteinuria which brings away protein chemically similar to but not identical with serum albumin. Clinically, there are three main components of the nephrotic syndrome: edema, with or without ascites; rarefaction of the long bones; susceptibility to infection. Bacteremia, due to pneumococci most often, may be and frequently is associated with a nephrotic crisis. However, crises can occur without a demonstrable infectious agent. A rapid rise in body temperature, sudden abdominal pain, pallor, and prostration are signs which led Farr to the term "nephrotic crisis."<sup>1</sup>

Kidney function tests such as urea clearance and ability to concentrate urine may yield results higher

than normal, normal, or lower than normal. There is very little correlation between such results and the extent of edema or of proteinuria. Quite often the urea clearance and the Addis-Shevky concentration test will be normal while there is a marked edema and proteinuria. Furthermore, though urea clearance may be altered in a crisis the direction of change, up or down, is unpredictable. Therefore, kidney function tests are not emphasized in the present paper, despite the fact that the onset of the disease sometimes shows up as a kidney dysfunction, and despite the fact that nephritis, in adults and older children particularly, can have its nephrotic phases.

Amino acids in nephrosis can be considered conveniently in three phases; in the chronic phases of the disease, in the crises, and in discussion relating to other aspects of nephrosis. These building units of the proteins are affected in all phases, but their chemical behavior (whether limited to the nitrogen-containing amino group or to the neighboring carboxyl, or acid, group, or whether both groups are affected) in this disease remains obscure.

## AMINO ACIDS IN THE CHRONIC PHASES OF NEPHROSIS

The subnormal concentration of amino acids in the serum of young patients during the less dramatic chronic phases of the disease has not been explained. What evidence there is, is of a negative kind. It is not due to failure to digest proteins or to absorb amino acids evolved from them in the gut. Farr and his associates tested the possibility directly by measuring the rise in amino acid content of the plasma after a meal containing protein and found that the extent and duration of the rise was what could be expected from normal individuals.<sup>2</sup> They also showed that it is not due to excessive fecal or urinary excretion of intact amino acids. Lyttle and his associates showed that re-absorption of amino acids by the renal tubules was not impaired, and that the rate of ammonia excretion was normal, the rate being doubled immediately after injection of a mixture of amino acids intravenously.<sup>3</sup> That evidence exonerates the gut and kidneys and directs attention to other condi-

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tions within the body. What of ascitic fluid and edema fluid generally? The importance of waterlogging cannot be judged well at this time, because measurements of the volume of interstitial fluid and blood have not been carried out simultaneously with analyses of amino acids. Hemodilution seems unlikely from observations on the hemoglobin concentration: when the numerical values of the changes in hemoglobin concentration, which for the purpose of calculation are assumed to be due to hemodilution and hemoconcentration, are applied to amino acids in order to refer them to constant concentration of hemoglobin, there is a subnormality of amino acids remaining. Against this view, Emerson and Beckman<sup>4</sup> report on a nephrotic child who quickly lost 6.5 kilograms weight as interstitial fluid, and simultaneously gained in concentration of the proteins and calcium in the serum until very nearly normal values were reached. In this child, waterlogging was definitely responsible for a major share of the pre-existing decline in protein and calcium concentrations. Unfortunately for the present argument, they did not report results of analyses for amino acids. Other, untested, possibilities may be mentioned before going on to consideration of diet. They are excessive conversion of amino acids to fatty acids in the liver, and excessive synthesis of short peptide chains instead of the long-chained peptides called proteins.

An optimal amount of protein fed to patients has been found to change nitrogen balance in their favor. While there may be an increased rate of building of tissue protein attending this change, the increase is not enough to meet all the demands of a rapidly growing child, for there is little or no change in concentration of serum albumin or of serum amino acids, even in the patient free from edema. The optimum protein ration for hospitalized patients was determined<sup>5</sup> to be about 3.2 Gm. of protein per kilogram of ideal body weight. Ideal body weight, computed from tables of height, age, and weight, was used for calculation in place of actual weight in order not to include the weight of edema fluid. From this work, the protein requirements of patients not in a hospital can be computed in terms of cuts of meat. The variation in protein content of cheeses, even of the same kind, denies their use for this purpose, since chemical analyses can scarcely be considered to be available to the home patient. Certain cuts of meat show a reproducibility of protein content justifying their use without continuous analyses. Veal, all cuts except viscera, is especially suitable; leg, loin, side of lamb, without tallow, are acceptable; pork, chuck ribs and shoulder, flank, and tenderloin are likewise accepta-

ble; beef, sirloin butt, second cut round, shoulder and clod make up one group, and heart and kidney another. Other meats, or other cuts, vary too much in their protein content to be suitable. For every ten pounds ideal body weight, the average nephrotic child needs daily quantities (in ounces) of any of the following: of veal, 2.75; the lamb group, 3; the pork group, 3; and the beef groups, 2.75 and 3.5. The weights refer to the edible portion of fresh meat. Whichever meat is chosen, the given ration should not differ by more than one-quarter of an ounce either way from that proposed. Lesser rations will be insufficient for the maintenance of positive nitrogen balance, whereas greater rations will impair, rather than stimulate, nitrogen metabolism. Amino acids in amounts equivalent in nitrogen can replace protein, without harm to the patient. Indeed, the claim has been made that intravenous alimentation with amino acids raises the tolerance of these children for protein by mouth.<sup>5</sup> It is obvious that the protein requirements alone are sufficiently strict to make proper treatment outside the hospital laborious and difficult; and certainly the biochemical investigation of the patient is more convenient in the hospital.

#### AMINO ACIDS IN NEPHROTIC CRISES

Nephrotic crises start and stop suddenly. Examination of hospital charts shows that crises start with a diversion of the body temperature curve and the curve of concentration of amino acids in plasma—sudden fever and falling concentration. The crisis stops, if the patient survives, usually two or three days later, with a return of these curves to each other. These sudden changes have not been explained. They are not due to hemodilution followed by hemoconcentration in so far as one can tell from the negligible changes in concentration of hemoglobin and other constituents of the blood. There is no evidence of excessive urinary excretion of alpha-amino acids.

Maintenance of the state of nitrogen metabolism cannot usually be left to normal channels of digestion and absorption, because of the severe gastro-intestinal disturbance and the prostration. Consequently, Farr and his associates<sup>6, 7, 8</sup> gave amino acids into the veins of the patients in crisis. Such therapy even when continued for a week induces no permanent change in concentration of proteins or amino acids in the blood after the crisis. The therapy is beneficial, however, as can be judged from mortality statistics. Before amino acid therapy, eight out of nine patients at the Hospital of the Rockefeller Institute for Medical Research died either in the first or in the second crisis.

Of eleven patients treated with amino acids by intravenous alimentation, each of ten survived at least two crises, and the other survived ten crises over a period of a year or more. The beneficial results were attributed to the amino acid treatment, though some of the benefit may be due to peptide present in the solution of amino acids, which was an enzymatic hydrolysate of casein. The nine or ten amino acids which have been shown to be essential for growth and maintenance of a positive nitrogen balance would be better tolerated and at least equally effective, according to the work of Rose<sup>9</sup> and of Madden and Whipple.<sup>10</sup> Whether administration of mixtures of pure essential amino acids would restore normal protein metabolism in nephrotic patients is conjectural at this time. It has been proved only in men and animals who were normally geared, so to speak, for synthesis of proteins. The success of other fluid therapy is controversial. Prior to amino acid therapy, highly potent type-specific antipneumococcus rabbit serum was used, and as noted, without effect on the outcome of crisis. One patient was given a transfusion of 500 cc. of blood during an attack, without apparent benefit. Once amino acids had come to be associated with benefit to the patient, concomitant control subjects to test the value of various fluids were not chosen, because the high mortality rate in crisis was too great a barrier psychologically.

During attacks the patients were fed the same quantity of protein, carbohydrate, and fat as during the chronic phases of the disease, so long as they could eat. However, the food was in liquid form, and fed on a four-hour schedule. Amino acids were given by vein in three or four doses per day of crisis, each dose containing 5 Gm. of amino acids in 50 cc. of sterile aqueous solution. The dry powdery casein hydrolysate, packed in vacuum sealed cans, was kept unopened in the ice box until needed. A portion was weighed, and dissolved in hot fresh triple distilled water at about 100° C. so as to yield approximately 5 liters of a 10 per cent solution. The solution was kept on the steam bath for 30 minutes to one hour, then placed in the ice box overnight. A large amount of flocculent precipitate was separated by filtration through a Seitz filter. The filtrate was bottled aseptically in lots of 100 cc., autoclaved, and stored in the ice box until used.

One of the hopes that comes with this therapy, or any other treatment tiding the patient over a crisis, is that enough patients will survive long enough to make possible a systematic investigation of the disease.

## DISCUSSION

Like so many aspects of renal disease, nephrosis is subject to widely differing opinions on good treatment and on cause. It is only fair to say that quite a few investigators do not favor amino acid therapy. However, their expectations often have been related to a permanent restoration of normal protein or nitrogen metabolism and not to the efficacy in nephrotic crises. As pointed out in this paper, these expectations have never had support from experimental evidence nor have they been claimed by those advocating the therapy.

The seriousness of the disease has been variously estimated. Heymann and Startzman<sup>11</sup> in Cleveland have reviewed the mortality data from American clinics and hospitals and believe that their present mode of treatment, which does not include amino acids, would be attended by a mortality rate of 15 to 20 per cent. Their estimate is the lowest proposed; rates as high as 70 per cent represent the experience of most observers.

The seriousness of a nephrotic crisis can hardly be overestimated, both diagnostically and prognostically. A crisis can present a very difficult diagnostic problem, as is exemplified by the following summary of a report taken from one of the medical periodicals. The report is about a patient with lipoid nephrosis complicated by pneumococcic peritonitis, who was admitted to hospital with puffy eyes, swollen belly, a pulse rate of 140 per minute, respirations at the rate of 30 per minute, and a temperature of 104° F. Immediate operation was ordered for acute perforative appendicitis with peritonitis. At operation, the surgeon observed a milky, oozing peritoneal fluid, from which was cultured pneumococcus type XXII. The peritoneum was smooth; no masses were felt; the ileum was normal. The surgeon removed the appendix, and the pathologist made a diagnosis of acute periappendicitis. During the almost three months interval required before ascites could no longer be detected, abdominal paracentesis was considered necessary on several occasions. The underlying nephrotic condition was apparently no worse than before the acute attack.<sup>12</sup> The signs and intensity of this reported attack, together with the knowledge that the patient had nephrosis, and the finding of pneumococci in the peritoneal fluid all point to a typical nephrotic crisis.

In seeking a step-by-step biochemical explanation of the progress of the disease and of the nephrotic crisis, one must admit that speculation is more plentiful than is fact. The present discussion of amino

acids shows this very well. The disease may be a derangement of general metabolism, as is claimed by some. Thyroid extract has been given on the basis that the supernormal concentration of lipids and cholesterol in the blood reflects myxedema.<sup>11</sup> On the other hand, Peters and Man<sup>13</sup> have reported that in these patients there is no correlation between basal metabolic rate and concentration of cholesterol in serum. Furthermore, they find no correlation between the cholesterol concentration and any single phenomenon in the disease. Finally, in contrast with myxedematous patients, the blood of nephrotic patients usually contains much more than normal amounts of neutral fats. Studies of the mobility of the serum proteins in an electric field reveal that the lipid globules are coated with beta-globulin.<sup>14</sup> Depending on the proportion of lipid material so coated, there is made possible a dispersion of lipids in the form of very small globules whose surfaces are soluble in serum. Quite frequently these suspensions have a refractive index very close to that of normal serum, and in this case the patients' sera may be translucent and belie the fact that the lipids are present in supernormal concentration. Though there is this intimate relationship of lipids and proteins physically, no physiologic correlation has been established.

Edema seems to be unaffected by amino acid therapy. But amino acids are not alone in their inability to favorably alter the electrolyte and water behavior. Intravenous administration of plasma is without consistent effect, for though striking results have been claimed by some, there are many more who fail to note any transitory or permanent relief by this therapy, either by diuresis or otherwise.<sup>15</sup> Indeed, spontaneous diuresis, of the kind noted by Emerson and Beckman,<sup>4</sup> though rarely so voluminous, occurs often enough in hospitals to make difficult a critical evaluation of diuretics, and may be attributable to simple rest in bed.

Other diseases of childhood appear not to affect the amino-acid content of serum, with the exception of pneumococcus pneumonia, in which there is a subnormal concentration at the time of onset and a return to normal upon recovery.<sup>16</sup> This interesting observation suggests that the pneumococcus may be the indirect agent for the subnormal concentration of amino acids in a nephrotic patient. The failure to demonstrate the organism as the infectious agent in a crisis does not preclude the influence of pneumococcic infection either in crises at other times or in the chronic phases of the disease in that patient.

The individual amino acids, especially those essential to growth, have not been tested separately in

regard to any aspect of the disease. That the deficit of amino acids in serum does not involve amino acids equally, is suggested by results obtained by means of two analytical procedures, differing in regard to the chemical groups of amino acids which they attack. On the one hand,<sup>17</sup> the amino group is attacked, with evolution of nitrogen, without affecting the carboxyl group; on the other hand, both the amino group and the carboxyl group are attacked, with evolution of ammonia and carbon dioxide. This procedure, the more specific for alpha-amino acids, was applied directly to plasma without removal of proteins.<sup>18</sup> The results obtained by means of the more specific procedure are usually lower, as might be expected on theoretical chemical grounds. During crisis the two methods yield closely similar estimates of amino acid concentration, as might be expected if the blood were depleted of certain amino acids more extensively than others. Many of the problems besetting children with nephrosis may be solved by this promising avenue of investigation.

#### BIBLIOGRAPHY

1. Farr, L. E.: *Am. J. Dis. Child.*, 58:939, 1939; also in Emerson, K., Jr., and D. D. Van Slyke: *J. Mt. Sinai Hosp.*, 8:495, 1942.
2. Farr, L. E., and D. A. MacFadyen: *Am. J. Dis. Child.*, 59:782, 1940.
3. Lyttle, J. D., E. Goettsch, D. M. Greeley, W. M. Grim, and P. Dunbar: *J. Clin. Invest.*, 22:169, 1943.
4. Emerson, K., Jr., and W. W. Beckman: *J. Clin. Invest.*, 24:564, 1945.
5. Farr, L. E.: *J. Pediat.*, 17:734, 1940.
6. Farr, L. E.: *J. Pediat.*, 16:679, 1940.
7. Farr, L. E., and D. A. MacFadyen: *Proc. Soc. Exp. Biol. & Med.*, 42:444, 1939.
8. Farr, L. E., K. Emerson, Jr., and P. H. Fletcher: *J. Pediat.*, 17:595, 1940.
9. Rose, W. C., and M. Womack: *J. Biol. Chem.*, 166:103, 1946.
10. Madden, S. C., and G. H. Whipple: *Am. J. Med. Sc.*, 211:149, 1946.
11. Heymann, W., and V. Startzman: *J. Pediat.*, 28:117, 1946.
12. Dobbins, J. M., and H. Rappaport: *Arch. Pediat.*, 59:646, 1942.
13. Peters, J. P., and E. B. Man: *J. Clin. Invest.*, 22:721, 1943.
14. Longworth, L. G., and D. A. MacInnes: *J. Exp. Med.*, 71:77, 1940.
15. Brown, H., C. H. Gray, and P. L. Mollison: *Brit. Med. J.*, 1:515, 1942.
16. Farr, L. E., W. C. McCarthy, and T. Francis, Jr.: *Am. J. Med. Sc.*, 203:668, 1942.
17. Van Slyke, D. D.: *J. Biol. Chem.*, 9:185, 1911; 12:275, 1912.
18. MacFadyen, D. A.: *J. Biol. Chem.*, 145:387, 1942.

# The Recognition of Acute Bacterial Endocarditis\*

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*Modern methods of treatment have altered the progress of bacterial endocarditis and greatly increased the importance of early diagnosis which is emphasized in this paper.*

Because of the amazing advances of recent years in the treatment of bacterial endocarditis, the terms *acute* and *subacute* have lost some of their accuracy in clinical definition. For example, the case in which a diagnosis of bacterial endocarditis due to *Streptococcus viridans* is made within a week or so of onset of symptoms and in which penicillin relieves all symptoms after a few days and effects a cure after a few weeks can hardly be called subacute. On the other hand modern therapy may so modify the course of endocarditis due to a *Staphylococcus aureus* or a *Streptococcus hemolyticus* that the term *subacute* could be applied more aptly than the traditional *acute*. For these as well as other reasons there is a tendency to use bacteriologic terminology exclusively for designating the varieties of endocarditis.

Nevertheless these time-honored terms retain a certain usefulness for teaching purposes. They call to mind differences in clinical course that were a matter of common experience before penicillin and other potent therapeutic measures came into use. The main differences between acute and subacute bacterial endocarditis are shown in Table 1.

TABLE 1

## *Differences of Acute and Subacute Bacterial Endocarditis*

	ACUTE BACTERIAL ENDOCARDITIS	SUBACUTE BACTERIAL ENDOCARDITIS
Bacteriologic	Strep. hemolyticus, Staph. aureus, pneumococcus, gonococcus, meningococcus	Mainly Streptococcus viridans
Pathologic	Usually no pre-existing heart disease	Usually pre-existing rheumatic or congenital heart disease
Mode of onset	Acute; often part of another obvious disease	Insidious
Course	Rapid	Relatively slow
Prognosis with treatment	Relatively poor	Good

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Excluding terminal or agonal endocarditis, which has no clinical significance, cases of acute bacterial endocarditis can be divided into two main groups. The first includes the cases in which the endocarditis occurs as part of the picture of a severe infection in some other locality than the heart, for example pneumococcic pneumonia, puerperal sepsis, gonococcic arthritis, meningococcic meningitis or others. The second group consists of cases in which the endocarditis is apparently primary. The problem of recognition of the endocarditis is somewhat different in these two groups. However, the diagnostic criteria are fundamentally the same and are based on four principal points, as shown in Table 2.

TABLE 2

## *Diagnostic Criteria in Acute Bacterial Endocarditis*

1. Septicemia
2. Embolic phenomena
  - a. In systemic circulation
  - b. In pulmonary circulation
3. Cardiac signs
4. Significant positive blood cultures

The term *septicemia* is used in a general sense to denote the picture of severe acute illness with prostration, fever, often attended by chills and sweats, tachycardia, petechiae, and hematologic findings usually characterized by leukocytosis, and progressive anemia. The composition of this picture varies somewhat with different types of infecting organisms. Consideration will be given to this point later. Of course the clinical manifestations are remarkably influenced when the bacterial endocarditis is an incident in the course of a serious infection like pneumonia or meningitis. The chief difficulty here arises from the fact that the possibility of endocarditis may not come to mind, since the primary infection may seem to explain the symptomatology. Furthermore, intensive treatment of the primary disease with a sulfonamide or an antibiotic may impair the chances of obtaining positive blood cultures. Suspicion of endocarditis may not be aroused until, after some days, it becomes obvious that a complication of the primary disease must be sought to explain the continued illness of the patient. An example of this course of events is given in Chart 1, which is a graphic presentation of the early part of the illness of a patient with pneumococcic endo-

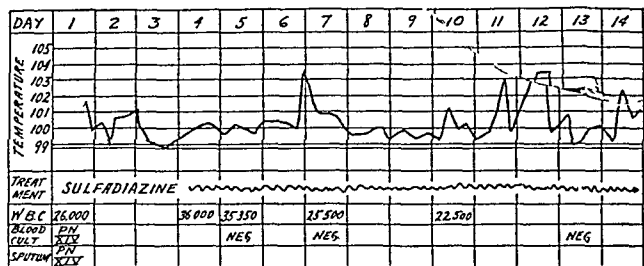


CHART 1. C. F. (B49953), 60 yrs., Pneumococcic pneumonia (R.U.L., L.L.L.), Pneumococcic endocarditis (Tricuspid valve).

carditis complicating lobar pneumonia. The pneumonia had developed five days before admission to the hospital. It is to be noted that the patient seemed to be improving with sulfonamide therapy until the latter part of the second week of hospitalization. At this time increasing prostration, chills, septic fever, and persisting leukocytosis indicated that there might be a complicating endocarditis, especially since the possibility of other complications seemed remote. The remainder of the patient's course was septic, and the blood culture yielded the Type XIV pneumococcus at the end of the third week of hospitalization. Purulent meningitis developed terminally, and the patient died in the sixth week of illness.

Since acute bacterial endocarditis usually affects the valves of the left side of the heart,<sup>1</sup> embolic phenomena are most commonly exhibited in the systemic circulation. Obviously, they modify the clinical picture variably, depending upon the size of emboli and the organs in which they lodge. There seems to be little excuse to elaborate further on this aspect of the disease.

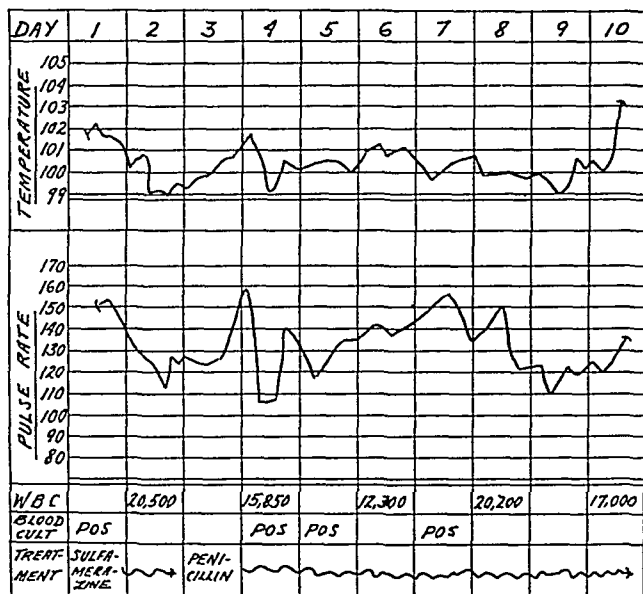


CHART 2. C. F., 25 yrs., Tricuspid endocarditis (Staph. aureus), Septic pulmonary infarcts, heroin addiction.

Involvement of the valves of the right side of the heart naturally predisposes to pulmonary embolism. Although this type of valvular involvement is comparatively rare, occurring in only 8.2 per cent of the 646 cases collected by Goldburgh, Baer, and Lieber,<sup>1</sup> there has been an unusually rich experience with right-sided lesions at this hospital.<sup>2-3</sup> In the past several years there have been 10 cases of acute bacterial endocarditis occurring as a complication of heroin addiction, and in all but one case the tricuspid valve was the seat of involvement. The following case reports exemplify this experience.

Chart 2 is the graphic record of a fulminating case of tricuspid endocarditis due to the *Staphylococcus aureus*. The patient was ill for only a few weeks altogether, was stuporous when admitted to the hospital, and had a rapid downward course. Her chest film (Fig. 1) showed numerous small pulmonary infarcts.



FIG. 1. Chest film showing multiple soft discrete opacities which represent septic pulmonary infarcts in a patient with endocarditis of the tricuspid valve due to *Staphylococcus aureus*.

Figure 2 is the chest film of a somewhat less fulminating case of the same kind. This film shows cavitation of the multiple pulmonary infarcts, a finding which is not uncommon in septic pulmonary infarction.

In these cases evidence of pulmonary embolism obviously was a valuable clue to the correct diagnosis. The clinical picture of septicemia, repeatedly positive blood cultures, and the finding of multiple pulmonary infarcts in a patient who has no evident source for pulmonary emboli in the systemic veins clearly implies the diagnosis of right-sided endocarditis.

Examination of the heart is helpful in the diagnosis of acute bacterial endocarditis only when a distinctive murmur, such as that of aortic regurgitation,

TABLE 3

*Variations in Clinical Picture of Acute Bacterial Endocarditis According to Type of Causative Organism*

	STREPTOCOCCUS HEMOLYTICUS	STAPHYLOCOCCUS AUREUS	PNEUMOCOCCUS	GONOCOCCUS	MENINGOCOCCUS
Previous valvular damage	60% of cases	50% of cases	About 40% of cases	Rare	Unusual
Other disease process	Portal of entry in 60%	Previous infection or pyemia in 66%	Pneumonia in 75%	Usually none	Meningitis in 50%
Joint involvement	Mild (25%)	Arthritis, variable (24%)	Rare	Arthritis in 66%	Mild arthralgia in 50%
Miscellaneous			Fulminating course; terminal meningitis		Skin rash; tertian, quartan, or double quotidian temperature curve

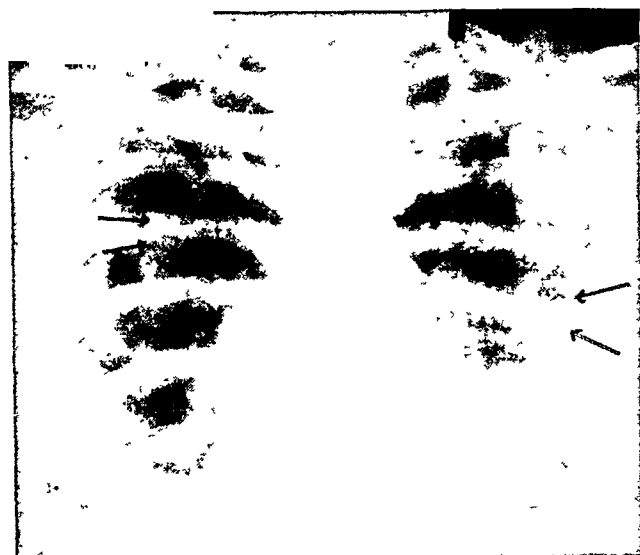


FIG. 2. Chest film in a case of tricuspid endocarditis due to *Staphylococcus aureus*. The cavities represent septic pulmonary infarcts which have undergone necrosis.

develops. The usual findings, however, are slight cardiac enlargement, tachycardia, and some kind of systolic murmur. These signs are not of much diagnostic importance because they may be expected to occur in any case of septicemia, whether or not there is endocarditis. Congestive heart failure is usually not a part of the clinical picture, except perhaps terminally. Rarely, however, manifestations of acute heart failure may predominate.

Although the diagnosis of acute bacterial endocarditis may be suspected before an organism is obtained from culture of the blood, it is rarely assured without this finding. Identification of the causative bacteria is usually possible even when treatment with penicillin or a sulfonamide is already under way. In addition, the finding of positive blood cultures under these circumstances is all the stronger evidence for bacterial endocarditis. Of course, identification of the causative organism is important also from the point of view of the plan for treatment.

The incidence of various bacteria in the etiology of acute bacterial endocarditis varies a good deal in the experience of different authors.<sup>4-8</sup> However, the main causative agents are *Streptococcus hemolyticus*, *Staphylococcus aureus*, the pneumococcus, the gonococcus, and the meningococcus. The variations in the clinical picture which are peculiar to each of these organisms are often of assistance in the recognition of the disease. These are shown in Table 3.

In conclusion, it may be well to point out that in years past the only advantage in recognizing acute bacterial endocarditis, aside from the academic satisfaction, was in being able to prognosticate imminent death. At present the prognosis is not so grimly hopeless, and it probably will improve further as experience enlarges and new remedies are devised. In a group of eight patients treated with penicillin at this hospital, there have been three recoveries.<sup>8</sup> Obviously, early recognition of endocarditis may have some value in improving the outlook for recovery and will certainly have a tremendous influence on the plans for therapy in any case.

## BIBLIOGRAPHY

1. Goldburgh, H. L., S. Baer, and M. M. Lieber: Acute bacterial endocarditis of the tricuspid valve, *Am. J. M. Sc.*, 204:319, 1942.
2. Hussey, H. H., T. F. Keliher, B. F. Schaefer, and B. J. Walsh: Septicemia and bacterial endocarditis resulting from heroin addiction, *J. A. M. A.*, 126:535, 1944.
3. Wilhelm, F., H. L. Hirsh, H. H. Hussey, and H. F. Dowling: The treatment of acute bacterial endocarditis with penicillin. To be published.
4. Thayer, W. S.: Studies on bacterial endocarditis, *Johns Hopkins Hosp. Reports*, 22:1, 1926.
5. Phipps, C.: Acute bacterial endocarditis, *New England J. Med.*, 207:768, 1932.
6. Williams, R. H.: Gonococcic endocarditis, *Arch. Int. Med.*, 61:26, 1938.
7. Tinsley, C. M.: Pneumococcic endocarditis, *Arch. Int. Med.*, 75:82, 1945.
8. Firestone, G. M.: Meningococcus endocarditis, *Am. J. M. Sc.*, 211:556, 1946.

# Short-Term Psychotherapy\*

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*Not all patients with psychoneurotic and psychosomatic disorders can be given extended psychiatric treatment and not all require it. Selection and proper treatment of the latter will result not only in satisfactory treatment for them, but opportunity for longer treatment for those who need it. The importance and effectiveness of such an approach as shown in actual practice is described in this paper.*

In psychiatric treatment there are usually several extremes in the customary approach to a case. There is a tendency now, during an era when psychoanalysis is popular, to think of treatment in terms of months or years if it is to be at all valuable, or to brand a patient as more or less hopeless or untreatable if practical difficulties stand in the way of long-term therapy. On the other hand, among psychiatrists who are unfamiliar with psychoanalytical theory and technic, there is a tendency to be careless and superficial about the methods of therapy, or go to the other extreme with the more drastic treatments such as shock therapy.

There is a type of case where a dependable middle ground can be chosen, and adequate and successful psychotherapy can be carried on in a fairly limited time. It is the case which is so difficult to diagnose correctly according to modern nosologic categories and which sometimes never comes to the attention of the psychiatrist until more serious symptoms have developed. This type of patient can occasionally be termed psychoneurotic; he will often have various physical symptoms and his illness falls into the classification of a psychosomatic illness. Such patients are often seen in the outpatient clinic of a large hospital and are usually in a fairly young age group. They are most often found, however, in a college or university setting and usually seek help from the campus psychologist, student counsellor or health service.

In another paper,<sup>1</sup> a series of 94 cases of college and university students was reported. These patients were all seen by the psychiatrists at the request of the Director of Student Health Service, University of Colorado. This present paper is a report on the type of problem presented by 70 of these students and an attempt to present certain short-term technics in psychotherapeutic interviewing as exemplified by certain selected cases from this group.

In this series of cases, there were 70 students, seen either on the Boulder campus during the weekly visits to the Student Health Service, or in the Psychiatric Liaison Department of the Colorado General Hospital.

TABLE 1

Sex	Number	Per Cent
Male	39	55.8
Female	31	44.2

TABLE 2

Class	Number	Per Cent
Freshman	27	38.5
Sophomore	18	25.7
Junior	16	22.8
Senior	4	5.8
Graduate	5	7.2

The cases were about evenly divided according to sex. The majority of the cases seen were in the Freshman class, with fewer in each succeeding class. This is entirely understandable; it is in the beginning of the college career that most personality problems present themselves and the time that most students need help. Also, students with personal difficulties more often drop out of college near the beginning and thus emotional troubles do not seem to be as prevalent among the more advanced classes.

TABLE 3

Referrals	Number	Per Cent
Student Health Phys.	54	77.2
Self	7	10.
Other Students	2	2.8
Teachers	2	2.8
Speech Dept.	4	5.8
Psychologists	1	1.4

As would be expected, the majority of students were referred directly from the physicians at the University Student Health Service, both of whom were thoroughly familiar with the type of problem needing psychiatric care. Because of the newness of the psychiatric consultation service, not many cases were referred from other departments. Seven students came in voluntarily seeking help because of some personal problem which had no medical significance and

\* From the Psychiatric Liaison Dept., Colorado University School of Medicine and Hospitals.

would not otherwise have been seen at the Health Service.

TABLE 4

<i>Disposition</i>	<i>Number</i>	<i>Per Cent</i>
Advised	23	34.8
Treated (I)	22	31.5
Treated (II)	25	35.7

The number of cases which were simply advised was large (34.8 per cent), but this was primarily due to the lack of time and personnel. Those in group I of the treated cases were simply given brief advice in one, two, or three interviews. Those in group II were seen in four or more interviews and were treated over a longer period of time. Only six or seven students were seen in ten or more interviews. Of the cases treated 40 or 85.1 per cent showed improvement. Of the seven cases not showing any improvement, one broke his appointment, three were constitutional psychopaths, one a lifelong stutterer with extreme emotional immaturity and one a severe psychoneurotic of 30.

Diagnostic categories \* include the following:

Emotional immaturity .....	14
Anxiety tension state .....	7
Other types of psychoneuroses .....	6
Psychosomatic condition .....	9
Simple personality problem .....	10
Schizoid personality .....	7
Schizophrenia (1 paranoid type) .....	5
Constitutional psychopathic personality .	8
Stutterer .....	4
Hysterical personality .....	3
Depression .....	4
Mentally retarded .....	1
Congenital spastic .....	1
Combat fatigue .....	2
Posttraumatic personality change .....	1
Psychomotor type epilepsy .....	1
Homosexual .....	1

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In considering this type of case, it is necessary to be familiar with the common emotional problems which confront the personality in adolescence and the late teens, specifically those most frequently encountered among college students.<sup>2</sup>

1. **Choice of a Vocation.** Many students surprisingly enough, have not the slightest idea why they are attending college. Many times they come with a

\* Diagnostic terms do not comply with the American Psychiatric Association diagnostic classification because in the majority of cases the condition was too mild to be classified in such categories.

† Some students were considered to fall under more than one classification, for instance, the boy with congenital spasticity was thought also to have a simple personality problem.

definite idea and find things much different than they expect and are disappointed. In order to be well adjusted and get the most out of advanced education, a person must first of all know what they're after and secondly, be fairly satisfied that they are going to get it by the method they have chosen. The basis of much personal insecurity among the students seen in this study was uncertainty about their college career.

2. **Sexual Adjustment.** Several types of problems related to sex usually are encountered. There are always a few students, male and female, who have no sexual knowledge, education or accurate information and are worried about masturbation, venereal disease, menstruation or sexual information in general. Many students become acquainted with promiscuity and petting for the first time and are in very troubling conflict about it. Many students are young and shy about heterosexual adjustments of any sort. In any college or university there are problems of homosexuality which eventually come to the attention of the visiting psychiatrist. The whole problem of sexual adjustment must be handled very delicately depending on the specific type of problem in each case. Preoccupation about these matters is often the primary reason for lack of attention and failure of concentration on studies.

3. **Emancipation from Family.** Many Freshmen are faced for the first time in their lives with leaving home. Sometimes it is an escape for them which they relish so much that they go "overboard" with newfound freedom. On the other hand, some have left home with some opposition from the family and have tremendous guilt feelings about their action. Often a student who has left a very sheltered home life will be faced with such an overwhelming burden of adjustment to new people, new political ideas, new religious concepts and be otherwise forced to adopt independent attitudes that he is completely inadequate to the situation and longs for escape to the protective custody of home and family.

## CASE HISTORIES

1. J. H.: A 20-year-old Freshman student was seen because of complaints of nervousness, insomnia, headaches, and inability to concentrate. She was depressed and bothered with feelings of uselessness and hopelessness about her college work and her future life. All of these symptoms developed in direct relation to the recent death of her Army husband with whom she was very much in love. She had heard of his death during the summer while she was working. When she decided to leave her job, her friends in the office persuaded her to begin college in the fall. She did so primarily because she and her husband had planned to go together, but she was without a very good idea as to what she planned to do in the future or what



kind of degree she wanted. She was also beginning to date again, and was having unconscious guilt feelings in relation to the development of an interest in one of her escorts which she felt was disloyal to her husband. She was advised during two short interviews which resulted in tremendous improvement and much gratitude and relief. She was told to work out her plans for four years of college only if she could be sure of her reasons for wanting a degree, to choose her subjects accordingly, and by all means to try to live a normal campus life. She was gently advised that dating and interest in the opposite sex was entirely normal and was encouraged not to cut herself off from it. Her feelings of guilt were explained to her simply, and her physical symptoms were interpreted as a result of anxiety and tension.

This case is typical of the group who needed only superficial guidance and simple advice and never failed to benefit markedly from one or two interviews. These cases are often neglected in a busy general practice because the internist does not take time to listen to the whole story; symptoms are thus accentuated and as Dr. Ebaugh says "calcified." With intelligent patients, an explanation which does not include a simple diagram of autonomic nervous system physiology is not satisfactory.

2. L. O.: This 22-year-old boy was a Navy veteran and had seen his diagnosis on his medical discharge papers, which said "schizoid personality." He came home after a rather severe emotional breakdown in the Navy and for some months was brooding and preoccupied with the term *schizoid*. He proceeded to look it up in dictionaries and psychology textbooks where he found further cause for dismay and confusion in such terms as *manic-depressive*, *introvert*, *homosexual*, *Oedipus complex*, all of which in some way he referred to himself. He came to college to study journalism and found that he was periodically depressed to the point where he could not concentrate on his work. This boy gave a history of a rather sheltered, puritanical, asocial upbringing on a farm. He found that Navy life presented many problems he was not prepared for and while at the Great Lakes Training School he became extremely melancholy, discouraged, nervous and frustrated. After a breakdown and hospitalization, his group went overseas and he was discharged. He had tremendous guilt feelings about being a quitter and letting his group down; he developed an antagonism toward the Navy psychiatrist and failed to discuss his problems. He was a very attractive, intelligent student and had many positive traits in his character which were emphasized and brought out as the interviews progressed. His guilt feelings were discussed repeatedly and he was told that rather than being a deliberate quitter, he was sick and ill-prepared for combat, that everyone was not a good risk and just because he could not adjust to the rigors of Navy life did not mean he could not make a good adjustment to civilian life. A semantic approach to his worry over the different diagnostic terms was employed with great success. He responded very well to common sense therapy and a logical, organized discussion of his problems, fears and shortcomings. He improved remarkably well during the six months of interviews and maintained his good adjustment after graduation. A re-

cent letter from him indicated some success in the field of journalism and plans to get married.

3. P. B.: A 20-year-old Junior who was seen over a period of two months of weekly interviews because of anxiety and many vague fears and crying spells. She was an extremely small but attractive girl who had been suffering with varying degrees of anxiety over a period of several years due to various conflicts concerning family problems, adolescent and sexual adjustments. She had fallen in love at 16 and for four years had been "going steady." This boy was drafted and left for overseas during this period; before he left they became engaged and on several dates had indulged in rather extensive petting, just short of intercourse. While he was away she had marked anxiety and guilt feelings concerning this activity, but later on transferred her feelings to the more benign worry over her social adjustment. Any situation in which the least attention was called to herself would immediately result in the most uncomfortable bodily symptoms typical of anxiety: flushing, palpitations, dryness of the throat, and inability to speak, a "sunken feeling in the pit of the stomach," and hot and cold sensations in different parts of the body. As a background for this was the parental picture. Her mother was a rather emotionally unstable woman who had had several "nervous spells" and told her daughter she had had the same fears while she was pregnant with the patient. Her father was an unusually successful but rather strict, irascible, and distant personality for whom the girl had almost a hero-worship type of feeling. Gradually, over a period of weeks, she obtained a great deal of relief by being able to discuss her fears and the personal problems to which they were related and when vacation time came, she was much improved.

## DISCUSSION

In any discussion of therapy, certain things must be kept in mind. First of all, the therapist must be adequately equipped to handle serious psychiatric problems, and trained in recognizing and dealing with cases of a serious psychotic or neurotic nature. He must be familiar with the various clinical patterns and diagnostic categories as well as with the fundamentals of psychopathology. This is absolutely essential in order to carry through the first principle of successful therapy: to possess enough knowledge to be aware of when *not* to use it. The possession of "a little knowledge" is indeed "a dangerous thing" when problems of personality are placed in the hands of unskilled persons as is so often true on college campuses today. Serious mental and physical disorders are masked by fairly superficial complaints which are often "red herrings" thrown out by the patient. These disorders are missed if the examiner is not aware of the possibilities in the background and equipped to look more deeply and recognize the true picture. Often, too, some simple personality problem is treated seriously over too long a period of time by an untrained worker and leads eventually to fur-

ther emotional upset and occasionally to more serious disturbance.

Secondly, the therapist must be personally in easy rapport with the type of problems presented and have the essential quality of a good physician, namely: empathy. This means simply the ability to enter into and experience the emotions and feelings of another person, the patient specifically. So many well trained, excellent therapists seem to feel that superficial personality problems and early emotional disturbances are not worth their time, and that if a person cannot be completely analyzed, he is not going to be helped. He must be able to look at the life of young people in a college or university environment with the eyes of youth and realize the intensity with which young persons are swept up into the busy life of a campus, and the characteristic problems they face at this particular time of life. Above all he must have that ability to understand other people's weaknesses and never give the impression of sitting in judgment or moralizing. Students, in fact all young people, will immediately withdraw if they feel their confidences are being betrayed by having the therapist pass a moral judgment on their behavior. Often the individual's main problem lies in the fundamental fact that he has never been accepted by anyone; a lifetime of chronic rejection beginning at birth is not a pleasant story and makes for extremely unhappy, sick, individuals. Often, as Dr. Spurgeon English has pointed out to us,<sup>†</sup> the therapist's job is simply to like the patient and to make him feel he is liked, that he has done a good job and that he is worth while.

Thirdly, the therapist must have some force of personality and a fundamentally solid philosophy of life in order to hasten the therapeutic transference which usually takes place and in order to more easily convince the patient of the value of certain positive attitudes and the reality of certain emotional experiences. Many of these teen age patients will be primarily worried about the state of the universe rather than immediate practical life situations. Some understanding of philosophical values and religious philosophy is essential in combating popular nihilistic and atheistic arguments which are all too astutely presented by these young people.

Fourthly, the therapist must have some well-tried therapeutic tools and a plan of work which is easy, quick and familiar to him. In the cases presented above, the improvement noted in most of them would have failed to take place if this fourth principle had not been observed. The limitations in time and per-

sonnel and the large number of cases referred was almost prohibitive to good therapy. First, it was necessary in one hour's interview to quickly sum up the situation and decide whether or not the case should be simply advised and sent away or diagnosed and referred elsewhere on the one hand, or whether he could be accepted for limited therapy. Only 68 per cent of the cases seen were accepted for treatment and only 35 per cent of them were seen over four times. It was therefore necessary at an early date in therapy to decide which cases had benefited enough from several interviews and could be dropped so that new cases could be accepted. Most of the follow-up interviews were only one-half hour in length.

Every physician's method of approach and manner of conducting interviews and personal relationships is an essentially individual thing. Psychotherapy in general cannot be taught or spoon fed. As the practice of medicine is in large part an "art" which has to be learned through personal experience and trial and error method, so it is with psychotherapy. However, certain principles are basic and essential to know at the beginning in order to perfect one's technic and properly treat patients. The approach used in most of these cases was for the most part based on the psychobiologic principles of the Meyerian school, with an understanding of the basic analytical concepts of personality defense mechanism, and can be outlined as follows:

### 1. OUTLINE OF THE PROBLEM

In these interviews, no formal history taking was done. The student simply came in, was greeted in a friendly, informal way, and was encouraged to state what his difficulties were in his own words, with as much freedom as possible for spontaneous conversation. Very occasionally leading questions would be asked especially to break the deadlock resulting from such statements as: "I don't know what's the matter; Dr. Holden wanted me to come see you." After the main features of the immediate difficulty were outlined, it was necessary to determine quickly whether this was a problem which could be handled on its own merits or whether it was a more deep-seated problem related to the patient's personality and emotional make-up as a whole. If the latter seemed to be true, the conversation for the next 20 to 30 minutes was guided gently to gain as much information as possible concerning the student's personality make-up and previous pattern of adjustment in family and community relationships. In this way, an overall thumb nail sketch of the student's problem and his personality could be arrived at without the lengthy

<sup>†</sup> Lectures in Psychosomatic Medicine, American College of Physicians and Surgeons, September 23-28, 1946.

procedure of taking a formal history. This was patterned greatly after the most commonly used draft board psychiatric examination in which the physician was expected to arrive at a fairly accurate judgment of the candidate's personality in 10 to 15 minutes.

## 2. ANALYSIS OF THE PROBLEM

At this stage, which usually took place in the first interview, the therapist made an attempt to weed out certain factors of immediate importance, to concentrate if possible on first things first, depending on the problem. If the case happened to be what seemed to be an open and shut case of untreatable personality disturbance or character disorder of long standing, the therapist took a definite stand about it at once, either to the patient himself, or to the relative if one happened to be available, but usually simply in the form of a report to the referring physician. It was necessary in this situation to make what were perhaps partially unjustifiable "snap diagnoses" in order to do the most in the long run for the patient who could be helped by treatment. In several cases, an initial impression of hopelessness in the matter of treatment was waived and the therapist brought the patient back for several interviews, only to discover that the time had been wasted and the diagnosis verified by further observation. Usually a Rorschach examination was very helpful in verifying the initial impression.

If, on the other hand, the treatment possibilities seemed fair, an early analysis of the practical features of the case was tentatively suggested to the patient and followed up in subsequent interviews. If the case was one of psychosomatic character, a brief explanation of the possible origin of the symptoms was given which was always readily accepted. If the case was tinged or loaded with anxiety, a brief explanation of the possible mechanism of anxiety was presented with the explanation that not much could be done about the symptom itself until more of the underlying problem could be studied. In other words, no patient who was accepted for treatment was allowed to go away from the first interview without the benefit of a good deal of reassurance from the therapist with a brief analysis of the possible factors involved as it seemed at that time.

At this point, one of the most important steps in therapy must be undertaken. The brief analysis given to the patient must be developed and enlarged upon for the therapist's benefit and an attempt made by him to formulate his plan of operation based upon his initial analysis of the problem. In the set-up described here, it was necessary to stick to a fairly rigid plan of procedure since it was impossible to visit

the university campus but once a week. However, if any patient was seen who seemed to be in immediate need of help, arrangements were made for the student to make the trip to the office of the psychiatrists in Denver during the week. In this way, allowances could be made for emergency cases where anxiety was so intense or the practical problem of such immediate urgency that a delay of one week might have had serious consequences. In two cases, immediate admission to the Colorado Psychopathic Hospital was advised and carried out. One case was a severe schizophrenic and the other was a depression with threats of suicide who later showed many features of schizophrenia.

## 3. REASSURANCE AND SUGGESTION

In this type of psychotherapy, a rather active role is taken by the psychiatrist in most cases. Except for an occasional case where there seems to be a pressing necessity for ventilation on the patient's part, the interviews are more or less directed and positive attitudes and directly practical solutions are suggested by the psychiatrist. Wherever indicated, the patient is allowed to express himself freely with the awareness that he has a helpful, sympathetic audience. Directions and suggestions are given with varying degrees of authoritativeness, depending on the maturity and independence of the student being treated. Most of the rather immature students seemed to react better to more positive direction rather than theoretical discussions about various possible outcomes. Always the therapist maintained a very confident attitude about the symptoms of the illness as well as the solution of the various problems, trying to instill that confidence in the student by repeated reassurance that (1) his symptoms were perfectly natural as a result of anxiety and nervous tension; (2) his case was not unusual and many other students had identical difficulties; (3) the anxiety and concomitant symptoms would clear up with the solution of the problem and (4) personality difficulties did not necessarily mean that a person is "queer" or "weak-minded" or "hopeless."

Free use of practical suggestion was employed. Suggestions and help as to choice of subjects, majors and career was given cautiously. Suggestions concerning daily routines, schedules and self-discipline in the matter of study were often necessary. Students who were too sociable, easy going and casual about their work, or who were having trouble concentrating and disciplining themselves to study, were given advice about daily schedules. Students who were shy, retiring, unsociable, were encouraged to give up some time to recreation and social activities in order to enlarge their horizon and circle of acquaintances. Stu-

dents who were having doubts and questions about religious attitudes were advised to attend certain group meetings and church services with which the therapist was familiar; these cases were carefully selected and the therapist made certain that the concepts expressed in these services were not of the sort which might add further to the confusion of the student. In certain cases it seemed necessary to provide for temporary outlets for aggression; one boy who daily lost his temper with his landlady and was in danger of losing his job as a hasher, was instructed to practice on a boxing bag in the gym every day and if necessary to curse it freely, using the name of the landlady whenever he felt like it. As Alexander stresses<sup>3</sup> in his book "Psychoanalytical Therapy," the principle of flexibility in treatment is applicable no matter what type of therapeutic school one happens to believe in; it is far more important to fit the technic to suit the nature of the case than to use some rigid method in every case.

#### 4. RE-EDUCATION

One of the therapeutic technics stressed by the analytical schools is encouraging the patient to relive and re-experience emotional feelings that have caused trouble in the past or that have been inhibited or repressed, so-called abreaction. This technic is invaluable but in the present situation is largely neglected because of the short time involved and the type of case considered. The next best thing is an attempt at "emotional re-education," in which the patient has a chance to look more objectively at his behavior and certain patterns of emotional reaction which have caused trouble in the past, re-evaluate them, and learn more adult patterns of behavior and more mature use of his emotions. He is given a chance to discuss his past life, his early strivings and his reaction to parental attitudes with a better understanding of the whole picture. The therapist takes the opportunity to point out evidences of infantile or immature behavior at the same time encouraging the patient in self expression and the development of self-confidence which will allow him wider limits of social adjustment. Any discussion of or emphasis on the patient's failures and liabilities are immediately followed up by a consideration of the patient's assets and past successes with a continued effort on the therapist's part to help the patient develop not only a more objective view of himself but also a more optimistic one. The emphasis is always on the practical, realistic approach to personal adjustments, and the patient is always brought back to the central problem wherever possible. Any handicaps, physical or otherwise, are al-

ways to cope with them quickly, and the patient is encouraged to consider adjustment as a choice or combination of the following two approaches. Wherever a personality problem exists, there is a failure of the person or ego to meet the demands of certain life situations. In the solution of the problem, one must either change certain factors in the situation, environment or other personalities involved, or make adjustments to suit the specific situation, always avoiding flight whenever possible. There are usually some factors which can be changed and the therapist, being an objective, mature individual, can often throw light on such problems where the patient has simply given up all hope. Wherever there are factors which are immutable, the therapist can often suggest new avenues of approach and adjustment that the patient has failed to consider.

#### 5. ESTABLISHMENT OF RELATIONSHIP

One of the most important and most intangible procedures often takes place without the therapist having a great deal to do with it deliberately. Probably the sine qua non for successful therapy on either a long- or short-term basis is the establishment of a good relationship between therapist and patient or a modification of the process usually referred to as transference. Often, the main need of a patient which is met by the therapist is the need of a friendly and stable human relationship. If the therapist is not able to enter easily into such a rapport, or to encourage the relationship with a shy, retiring type of individual, he may fail more often than not.

It must be remembered that one reason this particular type of therapy is so successful with the cases being considered here is that the general intelligence level among college students is naturally higher than average and the discussions are easily understandable. However, as stated in the beginning, the therapist must be able to recognize the more deep-seated type of personality disturbance in which mere "intellectualization" of the conflicts is not enough. These cases must be seen over a longer period of time, and the underlying conflicts must be ferreted out with the patient actually taking part in arriving at the interpretations and real emotional understanding of his problem. Such was the case in two of the stutterers seen.

#### SUMMARY

It is clear that there are a large number of cases in general practice, particularly those in a younger age group and in a college or university environment, who would benefit markedly from a limited type of psychotherapy given over a considerably shorter pe-

riod of time than is usually considered for psychiatric treatment. A discussion of limited psychotherapy is presented with case histories of students seen at the University of Colorado as examples. Although accurate and complete follow-up is not now available, there is some indication that many more serious types of mental and emotional disturbances may be prevented by early and clear-cut treatment.

### REFERENCES

1. Hunter, H., and M. L. Gorton: The Value of a Psychiatric Consultant to a University Student Health Service. To be published.
2. English, O. S., and Gerald M. J. Dawson: Emotional Problems of Living, Chapters X and XI.
3. Alexander, Franz, and Thomas M. French: Psychoanalytical Therapy, New York, Ronald Press, 1946.
4. Cottrell, Lillian: Psychological consideration in planning an educational program for adolescent girls, J. Health & Phys. Educ., December 1943.
5. de Berry, E. M.: A common type of emotional problem encountered among college students, Minnesota Med., 20:427 (July) 1937.

- Clements: The psychiatrist's place in college, Hygeia, 20:906 (Dec.) 1942.
- Fry, Clements: Mental Hygiene in College, New York, Commonwealth Fund, 1942.
8. Hinckley, R. G., and Anne F. Fenlason: Mental hygiene interviewing: a therapeutic approach, Am. J. Orthopsychiat., 12:309 (April) 1942.
  9. Raphael, Theophile: The place and possibilities of the mental hygiene approach on the college level, Am. J. Psychiat., 92:855 (Jan.) 1936.
  10. Raphael and Gordon: Psychoses among college students, Am. J. Psychiat., 95:659 (Nov.) 1938.
  11. Raphael and Himler: Schizophrenia and paranoid psychoses among college students, Am. J. Psychiat., 100:443 (Nov.) 1943.
  12. Weaver, M. M., and R. G. Hinckley: Students' health service experience in out-patient care of army students, Journal-Lancet, 65:311 (Sept.) 1944.
  13. Raphael and Himler: Manic depressive psychoses among college students, Am. J. Psychiat., 99:188 (Sept.) 1942.
  14. Wyler, Carl: Neurotic problems in a student practice, Journal-Lancet, 65:104 (March) 1945.
  15. Rogers, Carl R.: Counseling and Psychotherapy, New York, Houghton Mifflin, 1942.

## BOOK REVIEW . . .

**PRACTICAL MALARIOLOGY.** Prepared under the auspices of the Division of Medical Sciences of the National Research Council by Paul F. Russell, M.D., M.P.H., Luther S. West, Ph.D., and Reginald D. Manwell, Sc.D. 684 pp. with 238 illus. Philadelphia, Saunders, 1946. \$8.00.

There is no group of men in the United States better qualified to speak on the various aspects of malaria than the authors of this book. Doctor Russell was associated with the International Health Division of the Rockefeller Foundation as field director in malaria for nearly 20 years and worked in many parts of the world. When the United States entered the war, Doctor Russell was made head of malaria work in the office of the Surgeon General of the Army. Later, as Colonel Russell, he served as Chief Malariologist of the American Forces in North Africa and Italy.

In this book Colonel Russell and his colleagues have made use of the extensive experience of the International Health Division of the Rockefeller Foundation and other available official and nonofficial information including that of the armed services.

The book is divided into six sections in addition to an excellent history of malaria. Section III covers the pathology, clinical aspects, treatment, immunity, latency and relapsing malaria. Section IV gives an excellent discussion of the epidemiology of malaria. Section VI gives a discussion of the use of malaria as a therapeutic agent.

Although this book is the best and most complete presentation of the broad subject of malaria control, only a small portion (the sections mentioned above) will be of much interest to the busy general practitioner. The section on treatment is already out of date as some of the newer drugs developed during the war are not discussed. The major portion of the book covers the details of control programs and techniques which have been used in all parts of the world in attempts to control malaria. This book can be recommended as a reference for those interested in a coverage of the entire field of malariology.

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# Edema in Chronic Nephritis: Its Mechanism and Management\*

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*Chronic nephritis remains one of the chronic serious illnesses for which treatment is difficult. The author discusses the cause and mechanism of one of the primary symptoms of the disease and certain newer aspects and methods of treatment which have proved effective.*

## EDEMA

Edema is defined as a pathologic condition in which fluids accumulate excessively in the tissues or serous cavities of the body. It is brought about by a disturbance in the balance of forces which favor infiltration and reabsorption respectively. Edema fluid resembles plasma qualitatively but has quantitative differences. The sodium chloride concentration is frequently greater in edema fluid. Protein content, however, varies with the cause (acute diffuse glomerulonephritis—1 per cent; nephrotic syndrome—0.1 per cent; cardiac failure—0.5 per cent).<sup>1</sup> Three important factors control water metabolism of the tissues. These are capillary permeability, plasma protein concentration and capillary blood pressure. Capillary blood pressure tends to force fluids out into the tissues, osmotic pressure of the blood colloids tends to retain fluid within the circulation, and the degree of capillary permeability determines the ease with which fluids pass between the vessels and tissues.

Three general types of edema are recognized in discussing the subject of chronic nephritis.

1. In acute nephritis, increased capillary permeability resulting from a generalized vasculitis is thought to be the main factor in producing edema. As salts and colloids enter the tissues, they tend to bind fluids and thus an additional factor is introduced which increases the tendency to edema. Some element of hypoproteinemia also enters the picture due to loss of these colloids into the tissues. Finally, the hyper-

tension which so frequently is seen in acute diffuse glomerulonephritis increases arterial capillary blood pressure and adds an additional edema-producing factor.

2. In a nephrotic state, the marked proteinuria results in hypoproteinemia and lowered plasma osmotic pressure. This is the main factor causing edema in nephrosis. A similar mechanism is present in malnutrition, where the ingestion of proteins is reduced, and in hepatic cirrhosis, where the manufacture of proteins is impaired.

3. Cardiac failure not infrequently complicates chronic nephritis. In cardiac failure, increased venous pressure is the main cause of edema. This counteracts the osmotic pull of plasma colloids so that fluid is too slowly reabsorbed from the tissues into the circulation. Subsequently, when anoxia has been present for some time, increased capillary permeability results, introducing another cause for the production of edema.

There is a specific relationship between sodium and edema. Giving sodium chloride to an edematous person almost invariably increases the amount of edema. On the other hand, enormous amounts of sodium chloride may be ingested by a normal person without producing visible edema. Many believe, therefore, that the sodium intake produces visible edema only after the water regulating mechanism has been disturbed by one or more of the factors mentioned above. As little as 2 to 5 Gm. of sodium chloride may be a tremendous excess in edematous patients, whereas, normal individuals can ingest 20 to 30 Gm. It is the sodium ion primarily which causes edema to be increased under such circumstances. Without a source of sodium, fluid retention tends to be reduced. Salt-free condiments or flavoring agents (pepper, vinegar, lemon juice, onion, etc.), therefore, may be allowed to an edematous patient. For several years, there has been on the market, a vegetable salt which is advertised for patients with edema or tendencies to edema. The claims made for this salt are fallacious because it contains sodium mallate, and therefore, does not eliminate the offending sodium ion.

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## DIURESIS

Diuresis can be invoked in one of several ways:

1. Increasing glomerular filtration. The action of xanthine drugs is thought to be directly on the glomeruli, resulting in an increased filtration volume. Drinking large quantities of water increases glomerular filtration in normal persons. In the past, it has been felt that patients with renal damage would merely pass this excess amount of water into the tissues, and it has long been the practice to restrict fluid intake in chronic nephritis with edema and congestive heart failure. Recently, however, Schemm and others have proposed the use of a high fluid intake in the management of edema, provided salt is restricted to a minimum, and an acid-ash diet is employed.<sup>2,3</sup> Schemm feels that with decreased renal function, more water than normal is necessary to excrete waste products; this eliminates the need for having the kidney work at its maximum capacity.

2. Diminishing reabsorption in the tubules. This can be accomplished by introducing a nonthreshold substance which is excreted by the kidneys, such as urea. As this passes through the tubules it carries along a certain amount of water, thus preventing the reabsorption of water. The action of mercurial drugs is thought to be one of blocking water reabsorption in the tubules.

3. By decreasing abnormally high venous pressure. This method of diuresis only pertains when congestive heart failure is present. Digitalis and other accepted methods of therapy are employed. It is well to remember that there often is an element of cardiac decompensation in patients suffering from chronic nephritis with edema.

4. By increasing blood proteins. When hypoproteinemia is present, diuresis takes place following increase in plasma proteins. This method of therapy will be discussed below in some detail.

5. By other theoretical mechanisms. A water regulating center is thought to be present in the brain. When more knowledge of its physiology is available, it is conceivable that certain drugs may be capable of stimulating this center, thus inducing diuresis. No such method of therapy is known at this time.

## NEPHROTIC STAGE OF GLOMERULONEPHRITIS

When low-grade glomerular inflammation has persisted for some time, the constant loss of albumin in the urine results in lowered plasma proteins, with a reversal of the albumin-globulin ratio. Albumin, being a smaller molecule than globulin, has a

greater osmotic efficiency. Hypo-albuminemia, therefore, produces edema. The triad of albuminuria, hypoproteinemia and edema constitute the main clinical features of the nephrotic syndrome. A lowered B.M.R. is often seen in this condition. Some observers feel that the loss of body protein and its specific dynamic action, and the malnutrition are instrumental in lowering the metabolic rate. Actually, however, basal metabolism is normal in nephrosis; the apparent lowering is merely a mathematical illusion resulting from the increased weight and surface area produced by the edema fluid. The basal metabolism would be normal if calculated according to the patient's ideal weight. Increased blood cholesterol is also seen frequently in nephrotic syndromes, but the cause for this abnormality is not clear. Patients with the nephrotic stage of glomerulonephritis may progress into the chronic, azotemic or hypertensive stage with ultimate death from uremia, cardiac failure or cerebral accident. They may die of intercurrent infection such as peritonitis. Rarely, do they show a diuresis and improve. Prognosis for this condition, therefore, is not a bright one.

Bloom and Seegal have studied the nephrotic syndrome as to frequency, occurrence and differential diagnostic value in determining the nature of the renal lesion in patients who die of kidney failure.<sup>4</sup> They quote Baer and Christian who feel that every case of glomerulonephritis has a nephrotic element; and Loeb, Weiss and Fishberg, who found the nephrotic phase to be extremely rare in nephrosclerosis and pyelonephritis. Bloom and Seegal's postmortem studies of 120 patients tended to confirm the above impressions. Hypoproteinemia was found in some 80 per cent of 50 cases of chronic glomerulonephritis. Hypercholesteremia was found far more frequently in this group than in the remaining 70 cases. Severe proteinuria and edema were also more frequent in the glomerulonephritis cases, unless cardiac failure or malnutrition supervened in patients with chronic pyelonephritis. In none of the 50 cases of chronic glomerulonephritis did the nephrotic phase occur more than once; its duration varied between two months and five years (average 22 months). It is concluded, therefore, that the history of a nephrotic syndrome helps to identify a renal lesion as that of chronic glomerulonephritis.

Peters and Man have studied the interrelations of serum lipids in patients with diseases of the kidneys.<sup>5</sup> They find that hypercholesteremia bears no consistent relation to any single phenomenon of the disease, but is encountered most frequently in the presence of edema and, in certain instances, seems to vary with



the degree of water retention. Cholesterol may fluctuate greatly in the active nephrotic phase of nephritis. Malnutrition or inadequate diet, for example, may be responsible for a decrease in cholesterol. Hypercholesteremia is also irregularly correlated with hypoproteinemia. Since malnutrition lowers both albumin and cholesterol, an inverse relation between them cannot be obtained; nor does the cholesterol of the blood correlate any better with the degree of proteinuria or lowered basal metabolism. The factor in renal edema which appears to contribute to hyperlipemia, therefore, is unknown. It should be mentioned that there is no distortion of the cholesterol partition in these renal diseases, even though cholesterol in the serum is elevated.

### TREATMENT OF CHRONIC NEPHRITIS

The latent stage of chronic nephritis may be entirely asymptomatic or there may be slight albuminuria. The patient should be advised to forget his illness and live a normal, quiet life, avoiding exposure to cold and exhaustion. All foci of infection should be eradicated under the protection of sulfonamides. Dietary restriction is entirely unnecessary. If there is slight edema, this may be relieved by periods of rest with the feet elevated, and a salt-poor diet.<sup>6</sup> During the nephrotic stage of chronic nephritis, renal function is but slightly impaired, the chief therapeutic problem being to remove excess body fluids and replace plasma proteins.

### PLASMA PROTEIN REPLACEMENT

The hypoproteinemia of nephrosis should not be thought of as being limited to the vascular bed. It must be considered part of a derangement affecting protein stores all over the body. Likewise, the administration of protein contributes not only to the blood, but to the total protein pool. The size of this pool is enormous, and protein concentration, therefore, is not easily affected by the doses which can be administered to man. The ratio of extravascular protein to serum protein in a starved dog is 25:1. This means that 25 Gm. of protein must be administered to replace 1 Gm. in the plasma. This ratio is probably a bit smaller in human beings with nephrosis. Since the plasma volume approximates 3,000 cc., an increase of 1 Gm. in its albumin concentration represents a total of 30 Gm. of plasma albumin and a retention of 750 Gm. of protein in the body. Serum protein concentration may not accurately represent the total quantity of plasma protein because the volume of circulating plasma is variable. Diuresis may occur,

therefore, without any increase in serum albumin concentration (total serum albumin may be increased but the grams per 100 cc. remain unchanged, due to increased plasma volume). In the absence of plasma volume measurements, changes in the red cell count or hemoglobin may aid in interpreting sudden changes in plasma volume.

The administration of serum albumin in salt-poor form is the most logical procedure for replacing plasma proteins, but unfortunately this is not yet generally available to the practitioner. Serum albumin is a safe agent, except in the presence of severe hypertension and nitrogen retention, and in the absence of edema, where it may rapidly increase blood volume beyond the tolerance of the cardiovascular system. Repeated, small, daily injections are used (50 Gm. given intravenously at the rate of 10 Gm. per hour).<sup>7</sup>

The protein concentration in whole blood and plasma is relatively low. However, even though immediate and rapid reversal of hypoproteinemia is impossible, blood and plasma transfusions are not entirely valueless. With whole blood and plasma administration, we can at least compensate for the urinary protein loss on a gram for gram basis, and thus aid diuresis.

*Globin* is one of the components of hemoglobin. As far back as 1871, it was first demonstrated that hemoglobin could be split into hematin and globin by treatment with a strong acid. With the large amounts of cell residue left from the preparation of plasma, utilization of the erythrocytes and their derivatives is now feasible on a large scale. We know that 500 cc. of blood will yield 250 cc. of plasma and 24 Gm. of globin. Globin has a high colloid osmotic pressure; for example, 24 Gm. is equivalent in osmotic pressure to 600 cc. of plasma. Therefore, it is possible to obtain from a 500 cc. donation of blood, the osmotic equivalent of 1,200 cc. Globin is economical since it can be cheaply prepared from erythrocytes left over from the preparation of plasma. Strumia and his co-workers have reported on the properties of globin, and describe a case of chronic nephritis where globin administration resulted in a profuse diuresis.<sup>8,9</sup> Globin is administered intravenously as a 4 per cent solution made isotonic with glucose, 60 Gm. of globin being given daily for five days.

The *dietary* problem in treating patients with the nephrotic syndrome is a long range one. Protein intake must be increased to the point where urinary loss is exceeded, with the aid of eggs, cheese, meat, fish, poultry, gelatin and skimmed milk powder. A



normal individual requires 1 Gm. of protein per kilo of body weight in his daily diet. In the nephrotic syndrome, without azotemia, this may be increased as high as 2.3 Gm. per kilo of body weight in the daily diet. Anorexia may become a serious problem, and diets should be made as appetizing as possible. Salt restriction is very important, but the question of limiting fluids is a debatable one, as has been mentioned previously. The need for adequate vitamin intake requires no further comment. Amino acid mixtures are used by some to supplement dietary protein, but they have a bad taste. When given intravenously, they do not provide the colloid osmotic effects of protein solutions.

It is not uncommon to get a spontaneous regression of edema in nephrosis, so that it is often difficult to evaluate the effectiveness of any one form of therapy. Various *diuretics* have been employed in treating this disease. Urea is a nonthreshold substance and, therefore, is an active diuretic agent. It is given in dosage of 60 Gm. daily, but has the disadvantage of a very bad taste. Potassium chloride or nitrate, 5 to 10 Gm. daily, is also an effective diuretic. In the presence of renal insufficiency, however, there is the danger of retention of the toxic potassium ion. Ammonium chloride is also effective as a diuretic, given in dosage of 8 to 12 Gm. daily, but may precipitate a chloride acidosis. Mercupurin, given intravenously or intramuscularly (1 to 2 cc.) is a very effective diuretic, especially after a brief course of ammonium chloride. Its potential nephrotoxic effects are well known.

The use of *acacia*, first reported in 1933, has been revived recently.<sup>10</sup> In the past there have been many unfavorable reports which stated that acacia was ineffective in reducing edema or elevating plasma proteins, and that hepatic deposits of acacia produced tenderness and enlargement of the liver. Johnson and Newman used acacia intravenously, in 15 to 20 per cent concentration, in nine patients with the nephrotic syndrome. They encountered no hepatic enlargement, and believe that acacia is an effective and safe mode of therapy. Mild complications, such as slight fever, occasional chill and occasional vomiting were seen. It is thought that acacia mobilizes fluid from the tissues and thus enhances diuresis. Following the injection of acacia, there is an immediate increase in plasma volume due to this hydrophilic effect, so that plasma protein concentration is reduced (the total concentration of plasma protein is not affected, however). Goudsmit and Binger inject 500 cc. of a 6 per cent solution of acacia every other day for three to four doses. Each injection is given over a period of one hour, and the treatment

is supplemented with 9 Gm. of potassium nitrate daily.<sup>11</sup> Occasional urticaria, dyspnea or chest pain followed the injections, but no signs of liver damage were encountered.

*Concentrated human serum* was first used as a diuretic in 1938. The serum is concentrated four times. Aldrich and Boyle report a prompt diuresis and weight loss in 16 children with nephrosis.<sup>12</sup> They injected 25 to 65 cc. intravenously at two- to three-day intervals for a total of four injections. The mechanism of action is unknown; the injected serum may act as a continuous conveyor of water from the tissues to the kidneys. The diuretic effect of concentrated human blood serum is lost in the presence of any acute infection or hematuria.

### TERMINAL STAGE OF NEPHRITIS

Treatment of the terminal stage of chronic glomerulonephritis, with its dehydration, electrolyte imbalance, loss or retention of anions or cations, acidosis, azotemia and anemia, is beyond the scope of this paper. In passing, however, I wish to refer to Thorn's classic article "Physiologic Considerations in the Treatment of Nephritis."<sup>13</sup> He presents a simple plan of therapy based on a careful consideration of the agents required to correct the principal disturbances in body chemistry and physiology, stressing that quantitative as well as qualitative considerations require attention. I also wish to mention the influence of edema on clinical symptoms in the preterminal, azotemic stage. If the patient has a high degree of nitrogen retention with headaches, vomiting, drowsiness, etc., and is rendered edematous by intravenous injections of saline, there is frequently marked symptomatic improvement. This palliative therapy allows a certain degree of comfort during the last few months of the patient's life.

### INTERCAPILLARY GLOMERULOSCLEROSIS

In 1936, Kimmelstiel and Wilson first described this condition, and it is often referred to as the Kimmelstiel-Wilson syndrome. Since that time, reports as to the incidence and nature of intercapillary glomerulosclerosis have been conflicting. The pathologic distinction lies in the presence of dense hyaline material located in the glomeruli between capillary loops. These lesions are diffuse, usually involving most of the glomeruli to some degree, chiefly near the periphery of the glomerular tuft; often there is associated thickening of the afferent arteriole. Christian does not recognize intercapillary glomerulosclerosis as a pathologic entity.<sup>14</sup> He believes that all glomerular

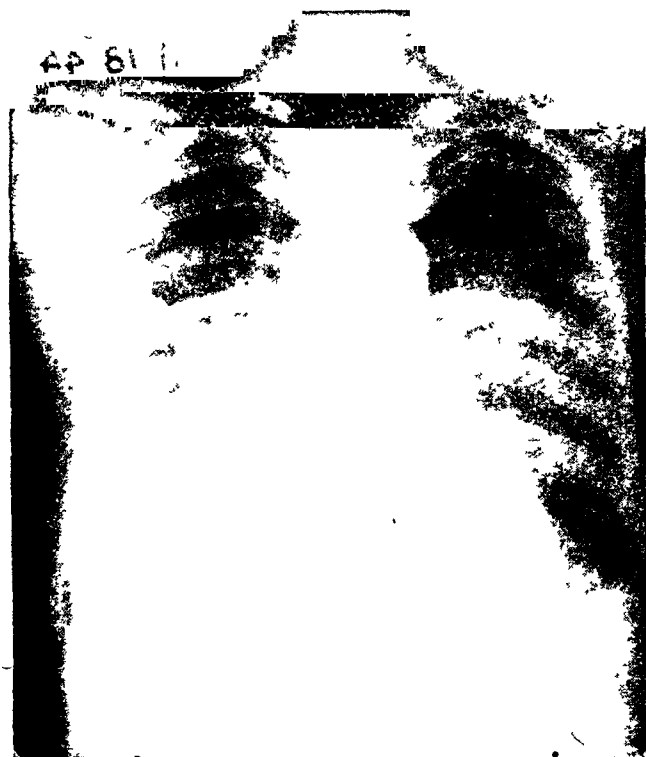


FIG. 1. Case of nephritis with mild azotemia, complicated by a right pleural effusion. Ultimate recovery with complete resolution of x-ray changes.

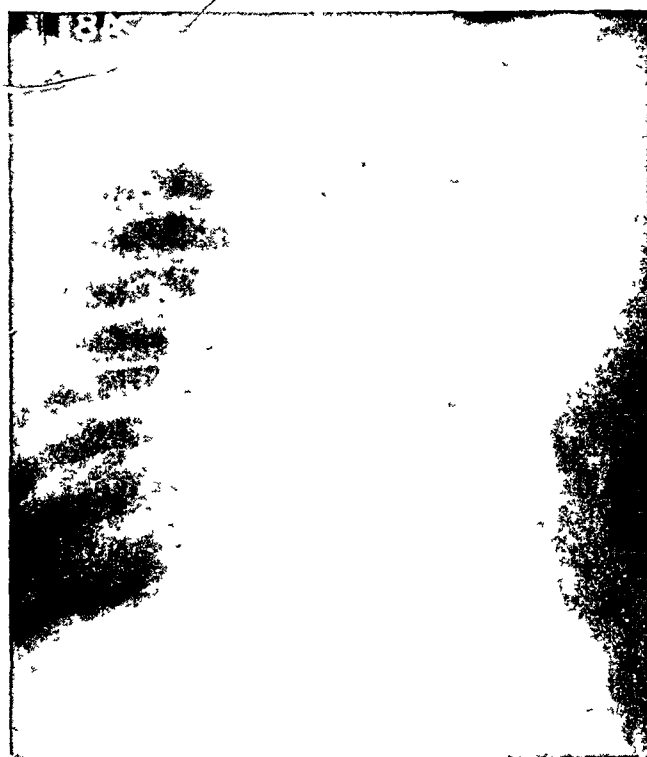


FIG. 2. Case of nephritis with severe degree of azotemia, complicated by left upper lobe pneumonia. Death occurred the day after this roentgenogram was taken.

lesions are nonspecific, and that clinicians rather than pathologists are to blame for describing types of glomerular lesions as diagnostic of a particular disease. Christian states that the various histologic lesions of glomeruli depend on the degree rather than the kind of injury inflicted upon them. He has described similar inflammatory, degenerative, proliferative and reparative processes in the glomeruli in uranium nitrate poisoning, *Streptococcus viridans* endocarditis, glomerulonephritis, pyelonephritis, eclampsia, "intercapillary glomerulosclerosis" and nephrosclerosis. This concept would explain the many similarities in the signs and symptoms of renal diseases.

Assuming that intercapillary glomerulosclerosis is a distinct clinical entity, the diagnosis should be considered in any patient who has mild or moderately severe diabetes mellitus for a considerable period of time (usually six years or more), and who begins to excrete moderate to large amounts of albumin in the urine associated with edema. Hypoproteinemia and hypertension are not essential parts of the disease, but frequently are present. Anemia is not an important feature, but there is usually widespread arteriosclerosis. The patients are usually over 45 years of age, more commonly females than males. The development of renal changes alters the clinical course of an

otherwise mild diabetes, leading to a serious and progressive illness. This is a type of nephrotic syndrome in which the causative lesion can be clearly placed within the glomeruli; the tubules are normal or merely contain some fat.

Siegal and Allen have made a postmortem study of 200 control cases, 100 of which had hypertension, and none of the kidneys showed this type of lesion.<sup>15</sup> In autopsies from 100 unselected diabetic patients, however, 33 showed this lesion in some degree. If these figures are correct, intercapillary glomerulosclerosis is a more specific pathologic finding in diabetes mellitus than hyalinization of the pancreatic islets. Goodof has reviewed the autopsy findings of 214 patients who were diabetics during life.<sup>16</sup> In his series 44 per cent showed the lesion of intercapillary glomerulosclerosis in a varying degree, while only 33 per cent showed hyalinization of the island of Langerhans. Goodof, however, did find such kidney lesions in about 10 per cent of control cases in a very mild degree. Laipply, Eitzen, and Dutra also conclude that intercapillary glomerulosclerosis is a common necropsy lesion in diabetics.<sup>17</sup> In reviewing the clinical findings, however, they found the nephrotic syndrome to have occurred in only 6.3 per cent of these patients.

## PULMONARY MANIFESTATIONS OF AZOTEMIA

In 1940, Scott, Schatski, and Bauer first reported on the roentgenologic appearance of pulmonary edema in acute glomerulonephritis without signs of cardiac failure.<sup>18</sup> Rendich, Levy and Cove further described this so-called "azotemic lung."<sup>19</sup> In azotemia, the roentgen films may show a symmetric, diffusely increased and irregular density in the central and basal lung fields. (Fig. 1, 2.) The density decreases gradually as it extends to the lung periphery, and the costophrenic angles are usually clear. The sites of predilection, therefore, are the actively arteriolized portions of the lung.

This infiltration is thought to be due to stasis in the large pulmonary vessels with transudation and exudation into the interstices and alveolar space of the lungs. There is no satisfactory explanation for this appearance of the lung in azotemia. Perhaps, the toxic factor which acts on the endothelial lining of blood vessels producing edema in nephritic conditions, may also be an etiologic agent in causing this type of pulmonary edema.

Pulmonary x-ray changes of azotemia occur in only a small percentage of patients with nitrogen retention. The degree of azotemia does not parallel the amount of lung changes, but the presence of these pulmonary changes is a poor prognostic sign unless the infiltration clears rapidly within a few days. On several occasions at this hospital, an "azotemic" appearance of the lungs has served as the first clue to the presence of renal disease. These findings, however, are not pathognomic, and must be corroborated by studies of the urine and blood chemistry.

### SUMMARY

Certain aspects of chronic nephritis and edema have been reviewed. When edema assumes a prominent role in the clinical picture of chronic nephritis, effective therapy is limited and prognosis becomes guarded.

### BIBLIOGRAPHY

1. Goldring, William: Lectures on Nephritis and Hypertension (New York University College of Medicine).
2. Schemm, F. R.: High fluid intake in management of edema, *Ann. Int. Med.*, 17:952 (Dec.) 1942; 21:937 (Dec.) 1944.

3. Leevy, C. M., J. A. Strazza, and A. E. Jaffin: Fluids in congestive heart failure, *J. A. M. A.*, 131:1120 (Aug. 3) 1946.
4. Bloom, W. L., and D. Seegal: Nephrotic phase: frequency and occurrence and differential diagnostic value in determining the nature of the renal lesion in 120 patients who died of renal failure, *Ann. Int. Med.*, 25:15 (July) 1946.
5. Peters, J. P., and E. B. Man: Interrelations of serum lipids in patients with diseases of the kidneys, *J. Clin. Investigation*, 22:721 (Sept.) 1943.
6. Bradley, S. E.: Management of chronic diffuse glomerulonephritis, *M. Clin. North America*, 29:1184 (Sept.) 1945.
7. Thorn, G. W., S. H. Armstrong, Jr., V. D. Davenport, L. M. Woodruff, and F. H. Tyler: Use of salt-poor concentrated serum albumin solution in treatment of chronic Bright's disease, *J. Clin. Investigation*, 24:802 (Nov.) 1945.
8. Strumia, M. M., F. W. Chornock, A. D. Blake, and W. G. Karr: Use of a modified globin from human erythrocytes as a plasma substitute, *Am. J. Med. Sc.*, 209:436 (April) 1945.
9. Strumia, M. M., A. D. Blake, and H. D. Cornman: Diuretic effect of globin in chronic glomerulonephritis, *J. A. M. A.*, 131:1033 (July 27) 1946.
10. Johnson, J. B., and L. H. Newman: Intravenous injections of acacia in patients with nephrotic edema, *Arch. Int. Med.*, 76:167 (Sept.) 1945.
11. Goudsmit, A., Jr., and M. W. Binger: Treatment of nephrotic edema, *J. A. M. A.*, 114:2515 (June 29) 1940.
12. Aldrich, C. A., and H. H. Boyle: Concentrated human blood serum as a diuretic in nephrosis, *J. A. M. A.*, 114:1062 (March 23) 1940.
13. Thorn, G. W.: Physiologic considerations in the treatment of nephritis, *New England J. Med.*, 229:33 (July 8) 1943.
14. Christian, H. A.: Non-specificity of glomerular lesions of the kidney, *Am. J. Med. Sc.*, 204:781 (Dec.) 1942.
15. Siegal, S., and A. C. Allen: Inter-capillary glomerulosclerosis and the nephrotic syndrome in diabetes mellitus, *Am. J. Med. Sc.*, 201:516 (April) 1941.
16. Goodof, I. I.: Inter-capillary glomerulosclerosis, *Ann. Int. Med.*, 22:373 (March) 1945.
17. Laipply, T. C., O. Eitzen, and F. R. Dutra: Inter-capillary glomerulosclerosis, *Arch. Int. Med.*, 74:354 (July) 1944.
18. Scott, T., R. Schatski, and W. Bauer: Pulmonary edema: its roentgenologic appearance in acute glomerulonephritis without signs of cardiac failure, *J. A. M. A.*, 114:613 (Feb. 17) 1940.
19. Rendich, R. A., A. H. Levy, and A. M. Cove: Pulmonary manifestations of azotemia, *Am. J. Roent. & Rad. Therapy*, 46:802 (Dec.) 1941.

### Life Expectancy Reaches New High

In 1946 the life expectancy at birth reached the all-time high of 65.6 years among American wage earners and their families, according to the statisticians of the Metropolitan Life Insurance Company. This represents a gain of more than a half year over 1945; it is more than five years greater than the figure for 1936 and nearly 19 years more than the life expectancy in 1911.

# Rocky Mountain Spotted Fever\*

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*Rocky Mountain spotted fever is a serious infectious disease, endemic in most of the states and of much greater practical importance than many have realized. Because of its high mortality rate under unfavorable circumstances or when improperly treated, early diagnosis and proper management are of the greatest importance. This full description of the disease with emphasis on management and treatment by an authority in the field is being published at the onset of the season when cases of this disease are most likely to appear.*

Rocky Mountain spotted fever is a severe generalized infection which must often be recognized and treated by general practitioners, since it is usually contracted in rural areas. The treatment of the disease, which must be based on its pathologic physiology, taxes the ingenuity of the physician to the utmost. The practical management of cases of the disease may be conveniently divided into three stages: (1) Before the appearance of the rash, (2) from the appearance of the rash to the peak of the disease, (3) convalescence.

## EPIDEMIOLOGY

Rocky Mountain spotted fever was described as early as 1873 soon after the first penetration of white settlers into Montana and the Snake River in Idaho.<sup>1</sup> For many years the disease was thought to be restricted to the Far West, but in 1931 its prevalence in the central and eastern states was recognized.<sup>2</sup> It has now been reported as endemic in at least 41 states. About 500 cases are reported yearly, with no increase from year to year.

**Organism.** The causal relationship between rickettsiae and Rocky Mountain spotted fever was established by Wolbach in 1919.<sup>1</sup> The rickettsiae are obligate intracellular parasites, and in this respect resemble the filtrable viruses. When stained by the Castellana or Giemsa method the rickettsiae are very small,

gram-negative, bacterium-like micro-organisms, which were originally described by Ricketts as "lanceolate chromatin staining bodies separated by a slight amount of eosin staining substance."<sup>3</sup> In spotted fever the rickettsiae frequently have a characteristic diplococcoid appearance. They are found in smaller numbers than in typhus, and occur in the nucleus of cells (Neel-Mooser reaction). In typhus the cells are distended with enormous numbers of organisms which are found chiefly in the cytoplasm.

Rickettsial diseases are primarily infections of arthropods; the tolerance of these vectors for the organisms suggests an ancient association bordering on symbiosis.

**Vector.** Rickettsial spotted fever is primarily a disease of ticks. The hard tick—the most common vector—may be infected at any stage of its life cycle.<sup>1</sup> Organisms have been demonstrated in the ova of ticks and found intranuclearly in all tissues of the tick, including the salivary glands and the intestine.<sup>3</sup>

Hard ticks live on moist ground covered with small bushes and shrubs, where numerous small and large mammals serve as hosts and as a source of blood for food. The larvae can fast for eight to twelve months, and the adults even longer; few larvae survive the complicated life cycle, however. Nymphs and adults hibernate through the winter. Ticks are long lived. *Dermacentor andersoni*, the wood tick, has been known to live three years.

In the West the vector is the wood tick, which is found in the Rocky Mountain region northward from New Mexico through British Columbia and western Alberta. East of the Rockies the principal vector is the dog tick, *Dermacentor variabilis*, which is most abundant on the Atlantic coast from Massachusetts to Florida. This tick may live in shrubs and beach grass. The list of proved or potential vectors includes eight other species of ticks.

**Reservoir.** In the West the chief hosts for the larval and nymphal forms of the tick are the yellow-bellied chipmunk and squirrel, although the large chipmunk, the woodchuck, meadow mouse, wood rat, and the white-footed mouse may also be infected.<sup>1</sup>

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The adult tick attacks principally cattle, sheep, and horses, but may also feed on smaller animals and on man.

In the East the hosts of the immature ticks are small rodents, chiefly field mice. The principal host of the adult tick is the dog, although cattle, hogs, horses, sheep, and practically all large fur-bearing mammals may be attacked. The dog appears to tolerate the infection surprisingly well.

**Transmission to Man.** Man is inoculated with rickettsiae by the adult tick when it obtains a blood meal. The percentage of adult ticks found to be infected has varied in different areas and in different seasons from less than 1 to 11 per cent.<sup>4</sup> The tick usually crawls about for one to two hours before becoming attached. The body temperature of the host and the blood meal somehow reactivate the rickettsiae so that they become virulent in two to eight hours. The rickettsiae usually enter the host through the salivary secretions of the tick, although it is possible to rub infectious fecal matter into the wound of the bite. Occasional cases of Rocky Mountain spotted fever have been reported to result from squeezing engorged ticks or removing ticks from pet dogs; presumably organisms from feces or blood entered through microscopic breaks in the skin. In the majority of cases a history can be obtained of an attached tick shown to contain blood.

In the West the disease is contracted during the months of March to July, when the unfed ticks become active after hibernation. The persons infected are those whose work or play takes them into tick-infested areas of the mountains. The disease is therefore chiefly one of adult males, especially ranchers, sheep-herders, and woodsmen.

In the East the period of greatest danger is from June to September, when the dog tick is most active, although occasional cases occur earlier in the spring and later in the fall. Ticks are likely to be most active in hot dry weather. The disease is most often contracted in suburban or rural areas and is frequently a hazard of recreation. In the East and South women and children are infected more often than men; in our experience many of the severe cases have been in small children.

The popular conception that spotted fever is more highly virulent in the West than in the East is due to an increase in the mortality rate with advancing years. The average mortality rate for patients under 40 is approximately 12 per cent, while for patients above that age it increases to about 40 per cent. Actually the mortality rate for comparable age groups is approximately the same in the East as in the West.<sup>5</sup>

The virulence of the organism varies from place to place in the same locality, and from year to year in the same place.

## PREVENTION

Preventive measures include personal prophylaxis against the tick and specific immunization. The control of the vector in nature is impractical with the present insecticides. No repellent has yet been marketed which is effective against ticks. Persons who work or vacation in tick-infested areas should attempt to prevent the tick from crawling up the legs or arms. High boots, leggings, puttees and socks worn over the trouser legs, and tightly buttoned sleeves are of prophylactic value, but some ticks will reach the body in spite of all precautions. Since ticks seldom attach themselves at once, and since the infecting agent is not activated for several hours, the body and inside of the clothing should be inspected at least twice daily. If a tick is found attached it should be removed immediately; a lighted cigarette held close to the tick usually will cause the tick to release its hold. Care should be taken not to squeeze or crush the insect if it is pulled off with the fingers. Cauterization of the bite is useless.

Vaccination with the specific antigen will produce active immunity. The original vaccines were prepared by grinding infected ticks;<sup>4</sup> a superior vaccine prepared from infected chick eggs is now available commercially.<sup>6</sup> To adults two doses of 2.0 cc. each should be given ten days apart; children under ten years of age should receive half this amount. The last dose should be administered at least a month before the patient enters an infested area. Vaccination after exposure is ineffective. Immunity is short lived, and the course of vaccine must be repeated each year. Individuals known to be intolerant to eggs, or with an allergic family or past history, should receive a preliminary skin test to the vaccine since anaphylactic reactions with collapse or urticaria may occur.

## NATURAL HISTORY OF THE DISEASE

The incubation period following the bite of a tick is from three to fourteen days. The prognosis is usually better with the longer incubation periods; the more severe infections usually have short incubation periods. The prodromal period of two to three days is accompanied by generalized nonspecific symptoms, which usually include headache, backache, irritability, malaise, anorexia, somnolence, chilly sensations, and photophobia. These symptoms resemble those of meningitis and of many virus infections—for example,

influenza and measles—and these conditions are among those which must be considered in the differential diagnosis. The onset of the disease is frequently sudden, with chill, severe frontal and occipital headache, intense aching of the lumbar region, upper abdominal pain, nausea, and vomiting. Chills and chilly sensations may continue. These symptoms suggest a blood stream invasion, and this actually is the case. The disease at this stage must be differentiated from a septicemia of other cause.

The characteristic rash develops one to five days after the definite onset of illness. At first the rash is macular; subsequently it becomes maculo-papular, and definite petechiae develop later.<sup>1, 4, 7</sup> The rash usually appears first on the ankles, wrists, and forehead, and spreads rapidly to all parts of the body. Within two to three days, it may be present on the palms, soles, scalp, inner cheeks, palate, and pharynx, but it is always more pronounced on the extremities. The rash initially blanches with pressure and may be confused with measles or other similar exanthems. In the milder cases, the rash tends to be discrete, but with increasing severity, the spots increase in size, becoming confluent and eventually purpuric. The initial color varies from pale to bright rose; the larger and more scattered the spots the brighter their color remains, and the better the prognosis. With time, the rash becomes darker and takes on a lavender tinge. Small or pinpoint spots that rapidly become darker indicate the severe type of infection and presage a poor prognosis. (Figs. 1, 2, 3 and 4.)

When the rash appears, the disease must be differ-



FIG. 1. Top: Eleventh day of rash in a severe case. Note the hemorrhagic character of the diffuse, almost confluent rash.

Bottom: Tenth day of rash in a mild serum-treated case. This eruption is the scattered, discrete papular type with little hemorrhage.

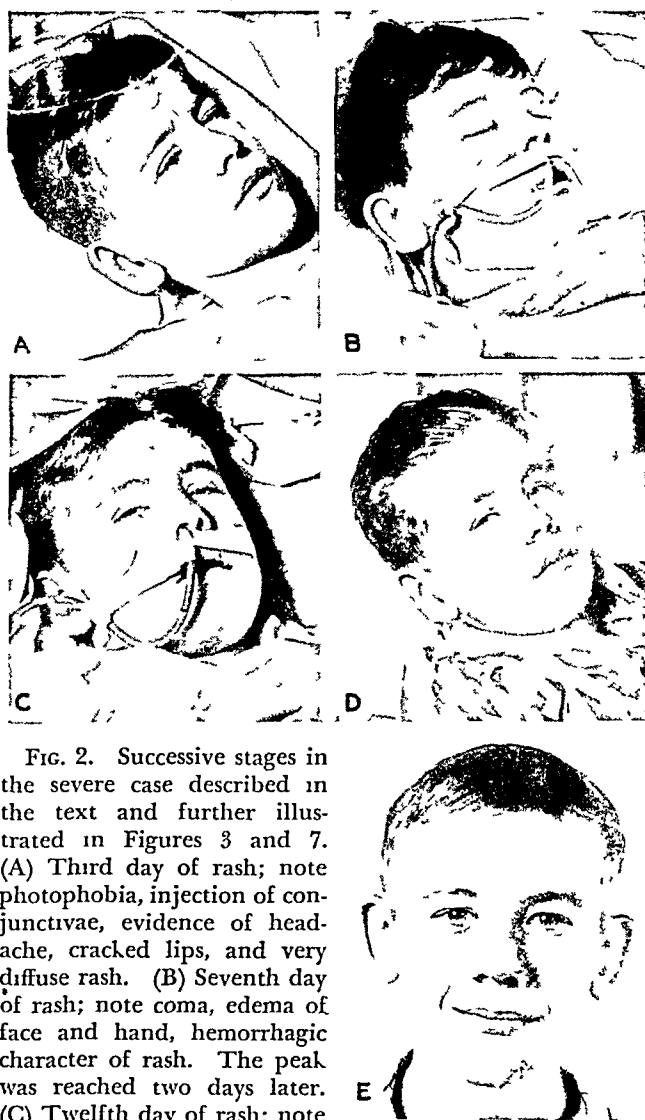


FIG. 2. Successive stages in the severe case described in the text and further illustrated in Figures 3 and 7. (A) Third day of rash; note photophobia, injection of conjunctivae, evidence of headache, cracked lips, and very diffuse rash. (B) Seventh day of rash; note coma, edema of face and hand, hemorrhagic character of rash. The peak was reached two days later. (C) Twelfth day of rash; note return of consciousness, persistence of edema, fading of rash. (D) Fourteenth day of rash; note increase in alertness, and decrease in edema. (E) Fourth month of convalescence; note residual stains of rash, and disappearance of edema.

entiated from meningococcemia, typhus, and typhoid fever. The rash in typhoid appears first on the abdomen and usually does not become purpuric. The rash in epidemic louse-borne typhus may greatly resemble spotted fever, but usually appears first on the abdomen, chest, and back, spreading to the extremities and head. The rash in endemic flea-borne typhus—the type usually seen in this country—is much less pronounced, does not become so hemorrhagic, and is frequently fleeting. The tourniquet test is usually positive in meningococcemia as well as in rickettsial spotted fever, but in the meningococcal infection the rash frequently becomes purulent and necrotic in the center within one to two days.

The rash is the visible evidence of the specific lesions which occur in small blood vessels as the organisms settle out during the septicemia.<sup>1, 4</sup> The rickettsiae are located intranuclearly in the cells of the vascular endothelium and smooth muscles of the arteriolar walls. As the endothelial cells proliferate, necrosis of the endothelium and smooth muscle cells occurs, and is followed by thrombosis. Lesions therefore occur in all parts of the body and are reflected by symptoms, signs, and laboratory findings.



FIG. 3. Interstitial edema in the severe case described in the text and further illustrated in Figures 2 and 7.

Right: Seventh day of rash; note edema and the hemorrhagic diffuse character of the eruption.

Left: Fourteenth day of rash; note the subsidence of edema, with wrinkling of the skin of the great toe and fading of the eruption.

The temperature rises abruptly within 24 hours after the onset of clinical symptoms. The febrile period usually lasts two to three weeks, but is quite variable. The maximum temperature usually persists through the second week, reaching 103° to 106° F. In fatal cases the temperature may rise above 106° F. More or less marked morning remissions are the rule. With recovery, the temperature usually falls by lysis.

The clinical course shows considerable variation, from abortive and mild ambulatory cases to fulminating cases with early death. Complications usually become evident by the time the disease reaches its peak. Convalescence is slow and complete recovery may require weeks to months, even in relatively mild infections.

## PHYSICAL FINDINGS

At the onset fever may be the only sign. With the appearance of the rash, other physical signs may develop. The occlusion of the venous circulation in the arm with a tourniquet or a blood pressure cuff inflated to the diastolic blood pressure for three minutes may elicit petechiae (Rumpel-Leede phenomenon) before they spontaneously appear in the rash.

In adults, early in the course of the disease, the pulse is full and strong, with a rate below that expected for the height of temperature; this disproportion may suggest typhus or typhoid fever. An abnormally high pulse rate from the onset is an unfavorable sign. The blood pressure is usually normal at the onset, but later becomes variable. It may drop suddenly should the patient go into peripheral circulatory collapse or have a massive hemorrhage. (Figs. 6 and 7.)

The respiratory rate at first is normal or slightly increased. A slight, nonproductive, bronchial type of cough is typical at the onset and is probably caused by the settling out of organisms in the filter-bed of the lungs. Râles may develop as a result of true rickettsial pneumonia, of pulmonary interstitial edema or of secondary bacterial pneumonia. Near the peak of the disease pulmonary congestion may result from myocardial failure. Myocardial failure must be carefully differentiated from peripheral circulatory collapse.

The conjunctivae are slightly bloodshot. Moderately to severely ill patients present a puffy interstitial edema, which may be generalized, or may be limited to the periorbital region or to the extremities; it is often difficult to detect early except by laboratory methods. (Figs. 2, 3 and 4.)

Severe prostration, mental confusion, dulling of the senses, restlessness, and hyperesthesia of the skin and muscles may be found early. The neck is usually slightly stiff and Kernig's sign may be present. The prostration increases and the patient becomes lethargic, with muscular twitching, fibrillary tremors, and abnormal neurologic signs such as ankle clonus and positive Babinski reactions. Because of the decreased intake of food and fluids which results from the mental changes, dehydration may develop rapidly, producing a dry tongue and a hot, dry skin. If motor activity is decreased because of stupor, local necrosis of the skin may occur at points of pressure.

The liver may be palpable but is rarely tender. The spleen becomes palpable late in the first week, and is usually firm and slightly tender. Constipation and distention usually occur, though peristalsis is not abolished.



FIG. 4. A severe case in a girl of four years on the 16th day of rash; the clinical peak of the disease occurred on the 14th day.

Top. Note the marked edema with closure of the eyes, and the mildness of the rash as compared with that on the extremities.

Bottom. Note the scattered hemorrhagic rash in the skin and the edema of the legs.



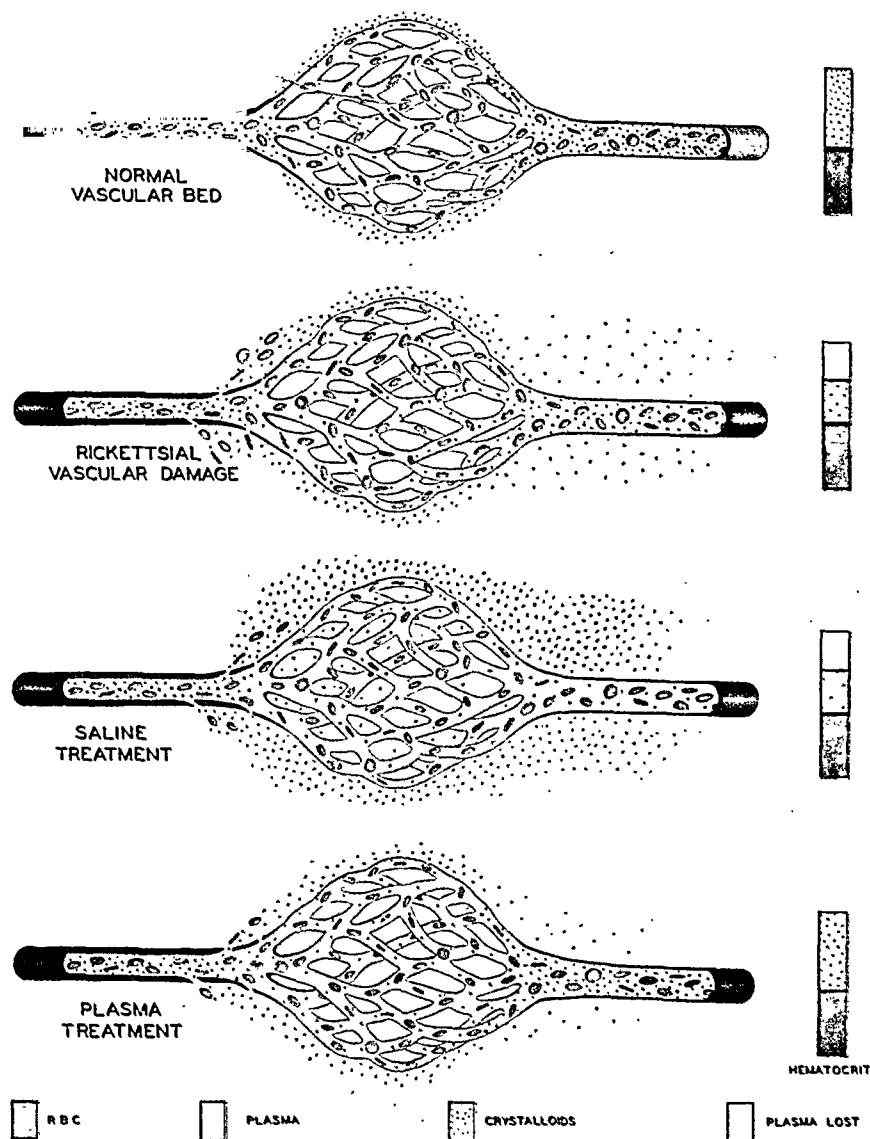


FIG. 5. This chart should be used in conjunction with those in Figure 6 on the opposite page. When the blood chemistry data in charts 6A and 6B are interpreted by the diagrams in this chart, the effect on the therapy given can be seen. By following one color from the diagnostic chemical data to the mechanism diagrams and back to the therapeutic data, one can observe the effect of crystalloids (blue), serum proteins (yellow) or blood (red).

The top diagram illustrates the normal extravascular crystalloid circulation. Pressure on the arterial side of the capillary bed (on the left) forces fluid out into the interstitial spaces. The fluid is reabsorbed on the venous side (on the right) by the colloid attraction of the intravascular proteins.

The second diagram illustrates the loss of integrity of the vascular wall from necrosis caused by rickettsial damage. Extravasation of erythrocytes produces the rash.

The third diagram illustrates the loss of additional proteins from the blood stream as a result of treatment by crystalloids. The crystalloids are then held outside the vascular tree by the protein which has been washed out.

The bottom diagram illustrates the reabsorption of crystalloids from the interstitial spaces by plasma introduced into the vascular system; the administration of plasma brings about the reabsorption by raising the intravascular osmotic pressure above that of the proteins still remaining outside the blood vessels.

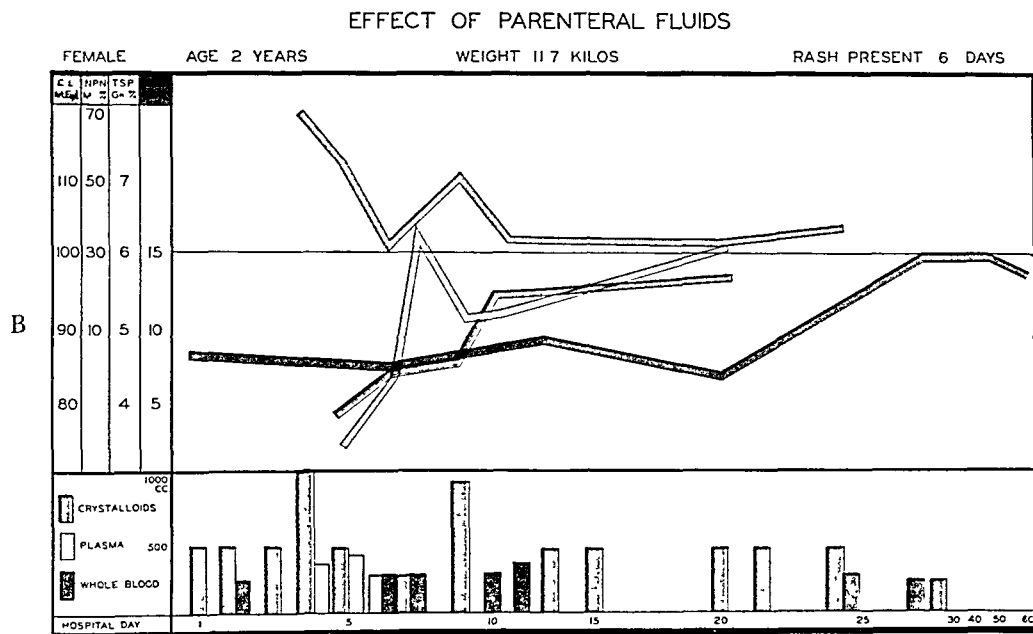
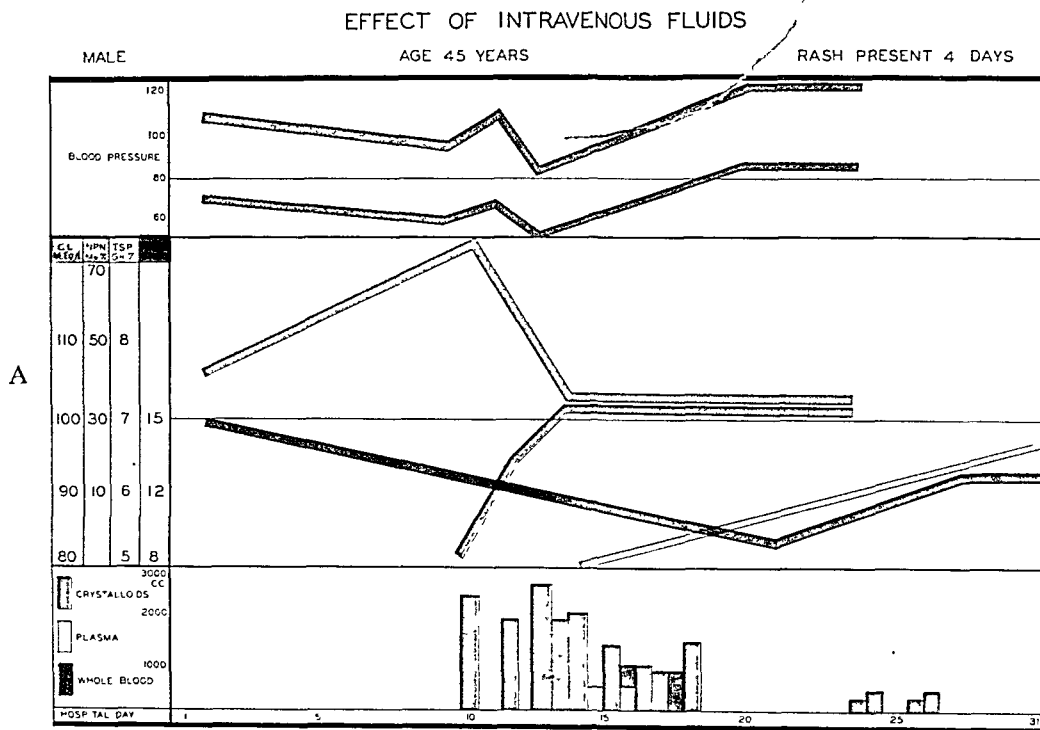


FIG. 6. Top (A): The harmful effect of giving intravenous crystalloids alone at the clinical peak of the disease is seen. Note the correction of the abnormalities in the blood chemistry (Cl, NPN), but the precipitation of "shock" with a drop in blood pressure; the administration of plasma and blood raised the blood pressure and the serum protein level.

Bottom (B): The beneficial effect of properly selected fluids is shown. Note the relatively huge amounts of fluids administered in relation to the weight of the patient. When plasma and blood were administered, crystalloids were given simultaneously with safety.

# ROCKY MOUNTAIN SPOTTED FEVER

## BOY AGE 14 SEVERE CASE

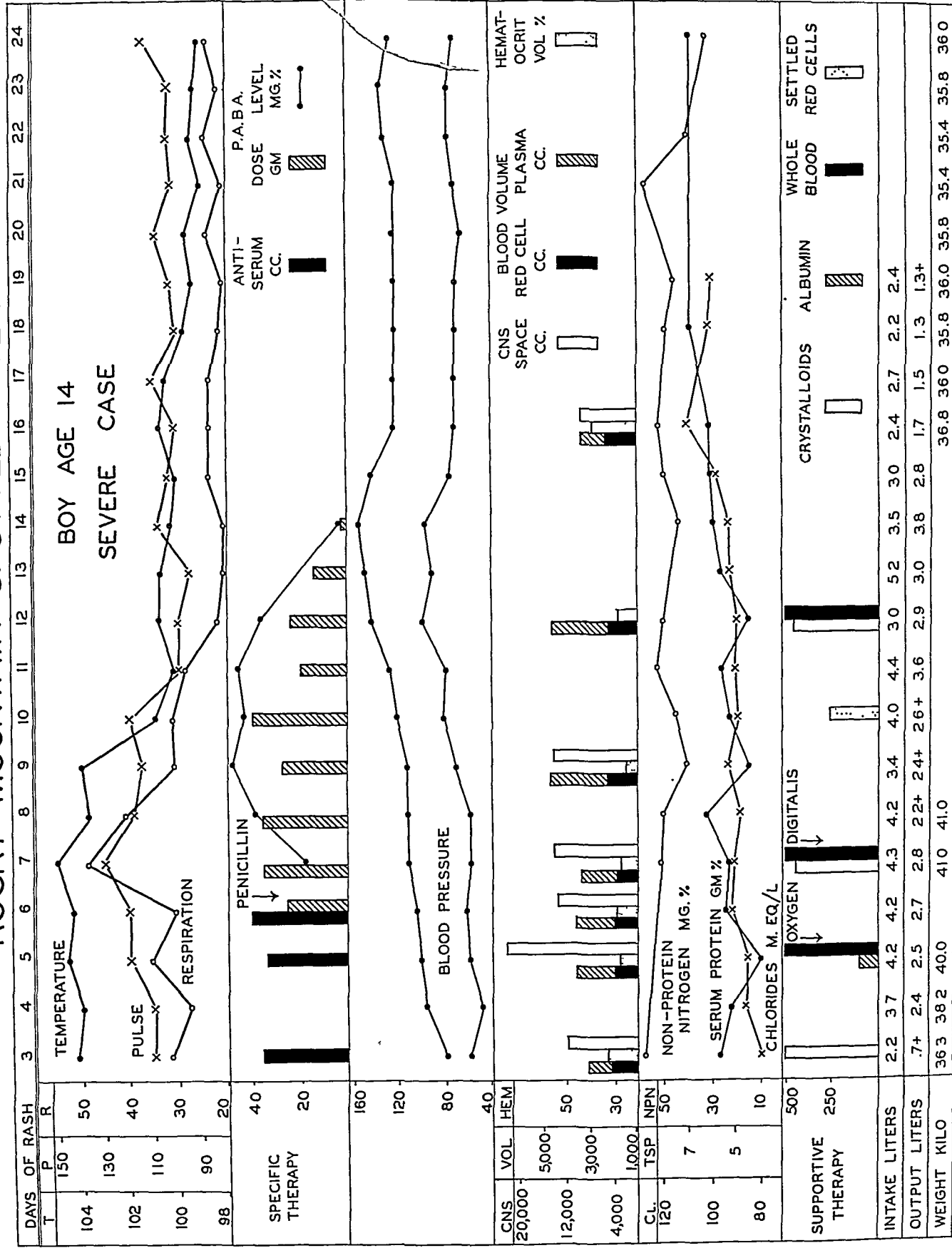


FIG. 7. Summary of findings in the illustrative case described in the text and shown in Figures 2 and 3.

## LABORATORY TESTS

**For Diagnosis.** No test is of aid in establishing the diagnosis early. Specific serotherapy or chemotherapy must be instituted on the basis of an accurate clinical diagnosis.

The most widely used diagnostic procedure is the agglutination of a strain of proteus bacilli by the patient's serum (Weil-Felix reaction).<sup>4</sup> The strain usually employed is proteus OX19. Agglutinins begin to appear during the peak of the disease, or early in convalescence, and progressively rise in titer. Three blood samples should therefore be taken: The first when the disease is suspected, another during the second week, and the third during late convalescence. A positive reaction is indicated by an increasing titer in dilutions greater than 1:160. The test is not specific and does not differentiate between epidemic or endemic typhus and Rocky Mountain spotted fever. The reaction apparently depends on the presence of an antigen common to rickettsia and the proteus bacillus; the antigen has been found to be a specific soluble substance, probably a polysaccharide.<sup>8</sup>

The complement fixation test is a specific aid for confirmation of the diagnosis.<sup>9</sup> The test becomes positive at about the same time as the proteus agglutination test, but sustains its high titer probably for years. A specimen of the patient's serum should be obtained as soon as the disease is suspected, and another during convalescence. The antigen is prepared from the yolk sac of infected chick embryos and is commercially available; its use requires very accurate serologic technic.\*

The rickettsiae do not grow in the absence of living tissue cells and hence cannot be cultured by ordinary bacteriologic technics. They may be grown in chick eggs by inoculation of the yolk, or in tissue cultures; apparently some ferment necessary for growth and reproduction of the organism is supplied by living cells.

The most accurate method of establishing the diagnosis which can be employed early in the course is by the transmission of the disease to male guinea pigs. However, this test is of academic interest only, since the results cannot be obtained soon enough to be of use in planning specific therapy.

**For Control of Therapy.** The hemoglobin and red blood cell count usually show little change until the disease is far advanced, when a normochromic anemia may appear. The decrease in red cells may be due to the debilitating effect of the disease, to specific para-

sitization of the cells, or to alterations in the circulating blood volume.

The white blood cell count usually ranges between 12,000 to 15,000. In our experience, however, leukopenia, with white cell counts of 4,000 to 6,000, has been quite frequent at the onset of the disease; the differential count then shows a neutropenia. As the disease progresses and leukocytosis develops there is an increase of polymorphonuclear cells which frequently show toxic granulation. The Schilling hemogram shifts to the left. Alteration in the total or differential white blood cell counts is not dependable evidence on which to base the prognosis or to suspect the development of complications.

The urine at the onset shows no abnormality. As the disease progresses slight albuminuria may appear, apparently as a result of the fever, and then disappear with convalescence. Occasional cases will show the alterations of acute nephritis, with greater albuminuria and with red cells and casts in the urine sediment. The urine volume may be reduced as a result of decreased glomerular filtration pressure or inadequate fluid intake.

The benzidine test for occult blood in the stool is frequently positive; occasionally gross bleeding or massive hemorrhage may occur as a complication.

The cerebrospinal fluid may be under increased pressure, especially when there is generalized edema. An increase in mononuclear cells is frequent and is evidence of the encephalitis which is so common that it may be considered part of the disease. The protein content of the spinal fluid is usually within the normal range—a finding which indicates that the permeability of the cerebral capillaries to protein may not be markedly increased.

In the first few days of the disease, blood chemical determinations are most often within normal limits. As the disease progresses, profound alterations in electrolyte balance and in protein metabolism usually occur.<sup>10-11</sup> The decreased intake of fluid and food, and the increased sweating caused by fever are reflected by a drop in blood chlorides. With decrease in the urinary output, the nonprotein nitrogen frequently rises. (Figs. 6 and 7.) A marked destruction of tissue protein is reflected in the greatly increased excretion of nitrogen in the urine. The depletion of tissue protein is reflected by a drop in circulating blood proteins which can be conveniently measured by the Kjeldahl, falling drop, or copper sulfate specific gravity methods. These procedures are within the facilities of the average small hospital. The mechanism of the changes in blood chemistry and their bearing upon the selection of therapy are discussed further below.

\* The complement fixation test will be performed on request of any physician by the National Institute of Health, Bethesda, Maryland.

The electrocardiogram occasionally will demonstrate myocardial changes. Peripheral circulatory collapse frequently develops independently of myocardial involvement and is accompanied by alterations in the blood volume as measured by the Evans blue technic. The fluid lost from the circulation is usually found in the interstitial spaces and can be measured by the thiocyanate method. (Fig. 6.)

Increased capillary fragility can usually be demonstrated by a simple suction technic utilizing a glass syringe, the barrel of a second syringe, and a mercury manometer. The blood platelets are within normal limits. The prothrombin time is usually normal early in the course of the disease, though it may become elevated if liver damage occurs.

Studies of kidney and liver function have demonstrated impairment of function during the acute phase of the disease, with recovery during convalescence.

### THERAPY

Therapy has a twofold purpose, and should be directed toward (1) control of the specific etiologic agent and (2) general support of the patient. Therapy must be correlated with the course of the disease, since measures which are helpful at one stage may be useless at another. The type of physiologic disturbance should be very carefully analyzed. Therapy directed toward acute circulatory collapse, for instance, may be definitely harmful in circulatory disturbance due to myocardial failure.

**Specific Therapy.** Until the diagnosis is definitely established by the appearance of rash, therapy should be expectant. Serotherapy and chemotherapy have not yet been shown to be effective prophylactically after tick bite and before the development of clinical signs. Specific therapy is most effective if begun before the third day of rash.

An effective hyperimmune rabbit antiserum, processed to concentrate the immune bodies in the globulin fraction, is commercially available.<sup>12</sup> The recommended dose is 1 cc. per kilogram of normal body weight given intramuscularly, though it can safely be given intravenously. In our experience the serum has been more effective if this dose is repeated daily for three days and if the initial dose is given before the third day of rash; if begun after this time, serum therapy causes little if any clinical improvement. Full therapeutic doses of serum given soon after the rash appears usually lessen the clinical severity of the disease and reduce the toxic symptoms.<sup>11</sup> (Fig. 1.) Though the processing of the serum reduces the number of hypersensitive reactions, patients should have a skin test or conjunctival test before it is administered.

Serum sickness may develop in the second week after injection and produce urticaria, joint pains, and a rise in fever. The uncomfortable symptoms can be reduced by aspirin given orally, and adrenalin injected subcutaneously; in some instances benadryl by mouth has been effective.

Since the rickettsiae are located intranuclearly, the ideal chemotherapeutic agent should be able to penetrate two cell membranes of the host. An agent which could be administered prophylactically after a history of tick bite, or early in the course of the disease before the rash is fully established would not have to penetrate cells. As yet no chemotherapeutic agent has been developed which is effective in all stages of the disease.

*All sulfonamides are definitely contraindicated at any time in the course of the disease, since their administration to human beings as well as to experimental animals has resulted in an apparent increase in the severity of the disease.<sup>13</sup> Penicillin has proved useless; streptomycin has not yet been proved to be effective.*

Para-aminobenzoic acid (PABA) has been reported to be useful in the therapy of rickettsial diseases. The trial of the drug followed the observation that sulfonamides increase the severity of spotted fever. Since PABA is known to be antagonistic to the action of sulfonamides, it was thought that it might have an opposite effect. The drug, which is a member of the vitamin B complex, apparently activates an enzyme necessary for growth and accelerates cell metabolism by increasing respiration. As a result, the rickettsiae suffer in the competition with the host cells and multiplication of the organism is thought to be hindered. The drug has been found to inhibit the growth of the organism in chick embryos, and to be effective therapeutically in guinea pigs infected with Rocky Mountain spotted fever.

The reported number of human cases of Rocky Mountain spotted fever treated with PABA is small. In one, an initial dose of 4 Gm. of PABA was given orally on the second day of rash, followed by 2.5 Gm. every two hours day and night in 25 cc. of chilled 5 per cent sodium bicarbonate; blood levels as high as 18.6 mg. per 100 cc. of blood were obtained.<sup>14</sup> The administration of the drug for four days was followed by a precipitous drop in temperature and a regression of signs and symptoms. We have administered as much as 60 Gm. (1.0 Gm. per kilogram) in 24 hours and have obtained blood levels as high as 58 mg. per 100 cc. of blood without apparent toxic symptoms which could be attributed to the drug. (Fig. 7.) The drug is rapidly excreted or destroyed. Effective ther-

apy, therefore, requires administration of an adequate dose early in the course of the disease with maintenance of a rather high blood level. Levels of PABA in the blood can be determined by the technic used for sulfonamides, since chemically the substance closely resembles these drugs.

The powdered drug is flocculent; it does not dissolve in ordinary liquids, and tends to clog up a stomach tube. Tablets of 0.25 Gm. are available, but these must be crushed and administered by tube to comatose or severely ill patients. Since the drug is a weak acid, administration of large quantities, especially in children, may result in acidosis, so that equivalent amounts of sodium bicarbonate or some other alkali should be given simultaneously. The plasma carbon dioxide combining power should be checked daily. It should be emphasized that PABA is still an experimental drug and that it should be used with care. The optimum duration of therapy and the indications for discontinuance of the drug are unknown. If the drug does increase cell metabolism greatly, the principles of supportive therapy outlined below must be followed even more closely.

Recently tablets containing 0.5 Gm. of the sodium salt of PABA have been marketed. It is also possible to obtain vials containing 2 Gm. of the powdered salt, which is the most soluble form.

**Supportive Therapy.** In uncomplicated cases diet and good nursing care are the most important factors in supportive therapy. Because of the alterations in protein metabolism, the intake of protein should be increased as soon as the disease is suspected, in order to prevent the development of full-blown protein deficiency.<sup>11</sup> The daily diet should contain 4 to 9 Gm. of protein per kilogram of normal body weight, depending on the age of the patient and the clinical severity of the disease. Because damage to the liver occurs in moderately severe or severe cases, the diet should also be low in fat and high in carbohydrate. Unless the total caloric intake is maintained, marked muscular wasting, with loss in weight, occurs as the disease progresses. The loss in flesh is usually masked by the generalized interstitial edema during the acute phase, but becomes evident during convalescence. We have observed adequately treated children, however, who not only maintained their weight, but actually gained weight during their illness.

The intake of all vitamins should be increased. Vitamins A, B<sub>1</sub>, C and K should be given in full therapeutic dosage because of their possible effect on infection, shock, capillary fragility, and bleeding tendency, respectively. Niacin should be given in the form of the amide, since niacin itself (nicotinic acid) may not be methylated in the presence of liver damage.

In the first few days of illness the patient will take some food and fluid by mouth. If he becomes delirious, comatose, or unco-operative and the desired intake is not attained, the diet should be supplemented or replaced by high protein liquid feedings. If necessary, either adults or children can be maintained with gavage feedings every two hours given through a large caliber nasal tube left constantly in the duodenum. A formula which has proved satisfactory in our hands is as follows:

Skimmed milk	850 cc.
Powdered milk	100 Gm.
Corn syrup	75 Gm.
Concentrated fish oil	20 drops
Niacinamide	100 mg.
Ascorbic acid	500 mg.
Thiamine chloride	15 mg.
Riboflavin	10 mg.
Menadione	1 mg.

This amount contains 115 Gm. of protein, no fat, 118 Gm. of carbohydrate, 932 calories (0.9 per cc.), and adequate vitamins. If the caloric intake must be increased, the substitution of whole milk for the skimmed milk will add 34 Gm. of fat; the formula will then contain 1,238 calories (1.2 per cc.). The mixture thickens upon refrigeration and should be warmed to body temperature before administration. It has a consistency and flavor similar to malted milk; the addition of chocolate syrup makes it sufficiently palatable to be drunk from a cup. When gavage feedings are used, the tube should be washed out with water after each administration of food or medicines. It is wise to change the tube from one nostril to the other at least every 48 hours; the nose and pharynx should be rested several hours before reinsertion.

As the disease progresses, alterations in capillary permeability become evident. In the normal vascular bed plasma will not pass through cell membranes, but water and crystalloids, such as chlorides or urea, will pass freely both ways. When the vessels are damaged, the permeability is altered and protein molecules leak out into the tissues. As crystalloids also pass out, they are held outside the blood vessels by the protein molecules and the plasma volume is thus reduced, although the number of circulating red blood cells may remain exactly the same. This condition is reflected by a rise in the hematocrit. The decreased fluid intake and urine output, plus the loss of fluids by sweating (which may be aggravated by the administration of aspirin) will frequently lead to prerenal azotemia, with nonprotein nitrogen values of 70 to 90 mg. per 100 cc. At the same time the chlorides may be reduced to 75 to 85 milli-equivalents

per liter. This degree of disturbance in the blood chemical findings demands attack. The administration of glucose and saline will cause the blood chemical values to return to normal, but the altered capillary permeability permits additional plasma to be washed out. The circulating plasma protein may thus be reduced sufficiently to alter osmotic equilibrium further and to allow more crystalloids to remain outside the blood vessels. This vicious cycle leads to peripheral circulatory collapse (medical shock). (Fig. 5.) The serum proteins have been found to drop precipitously in such instances; the circulating blood volume is decreased, and the available fluid space increased.

If the plasma proteins are found to be low or falling rapidly, or if a drop in systolic and diastolic blood pressures gives evidence of impending circulatory collapse, preformed protein should be administered. Intravenous replacement therapy in the form of purified albumin, plasma, or whole blood increases the intravascular osmotic pressure sufficiently to allow crystalloids to be given safely. Not all the replaced protein will be retained in the blood stream, but some crystalloids will be reabsorbed into the blood vessels on the venous side. A very large amount of preformed protein may be required to restore the circulating blood volume and blood constituents to normal. We have administered as much as 2,800 cc. of whole blood and plasma in a period of ten days to a two-year-old child weighing 11.7 kilograms (Fig. 6), and 2,500 cc. of plasma in 36 hours to a 15-year-old boy.<sup>10</sup>

Concentrated serum albumin (25 Gm. per 100 cc.) is a very powerful osmotic agent, and can increase the blood volume 14 cc. for each gram administered.<sup>15</sup> Its advantage lies in its small bulk and low salt content, though its mode of action is the same as that of the more widely available plasma. If the hemoglobin or hematocrit indicates a reduction in red cells, whole blood would be preferred. The type and quantity of parenteral therapy given should be governed by clinical judgment and by careful laboratory control. The efficacy of supportive treatment should be checked by repeated laboratory determinations to be certain that the desired results are being obtained. The total serum proteins may have to be determined at three- to eight-hour intervals during critical periods.

Because of the possibility of myocardial damage in addition to peripheral circulatory collapse, the quantity and speed of administration of parenteral fluid should be carefully governed to avoid overloading the circulation and precipitating acute central (myocardial) circulatory failure and pulmonary edema; this danger is more likely if albumin is used. If in doubt

it is probably better to under-treat than to over-treat the patient. The administration early in the illness of the high-protein diet described above has reduced the amount of preformed protein necessary for support of the circulation. In the long run the patient must still cure himself. No supportive therapy will be helpful unless the patient's powers of repair are capable of overcoming the vascular defect.

Temperatures above 104.5° F. (rectal) should be controlled by cold packs and the administration of antipyretics, since continued hyperthermia may cause irreparable damage to the brain. Cold packs may increase the danger of a complicating pneumonia, and possibly should be accompanied by the prophylactic administration of penicillin. Aspirin increases sweating, causing loss of chlorides and vitamins; if large amounts are given it may also produce acidosis. While it is being administered the blood chloride level and plasma carbon-dioxide combining power should be carefully followed.

Oxygen therapy should be given by a nasal tube, facial mask, or oxygen tent as soon as impending circulatory failure, pneumonia, or myocardial failure is suspected. If the administration is withheld until cyanosis is deep and the indications obvious, irreparable damage may have been done.

### COMPLICATIONS

In our experience the most serious complications have been circulatory failure and pneumonia. Circulatory failure is more likely to occur between the eighth and fourteenth days, and may be peripheral or myocardial in origin. The mechanism by which peripheral circulatory failure develops and the principles for correcting it have been discussed above. Myocardial failure may result from involvement of small coronary arteries or from actual invasion of the heart muscle by rickettsiae (although this occurrence is more common in scrub typhus), or the myocardium may be pushed beyond its functional capacity by overzealous fluid administration. Impending myocardial failure can be recognized by a rise in pulse rate, the occurrence of a gallop rhythm, and an increase in venous pressure, which is noted first in the neck veins and can be confirmed by direct intravenous measurement with a spinal fluid manometer. The presence of a gallop rhythm or venous engorgement is an indication for digitalization. Digitalis should be administered with caution since a myocardium damaged by infection is probably more sensitive to digitalis than one failing from purely mechanical reasons. If the failure is acute and is accompanied by pulmonary edema, purified glucosides of digitalis or strophanthin should be given intravenously. Rarely, in patients

who have evidence of chronic rheumatic heart disease, rickettsial infection will produce electrocardiographic changes—such as an increase in the PR interval above 0.20 seconds—which are indistinguishable from those caused by a reactivation of acute rheumatic fever.

Pneumonia may be due to a true rickettsial invasion of the lungs; in this type sputum will be scanty and not purulent. If pneumonia develops, irradiation over the lungs could be added to the specific therapy described above. More commonly pulmonary congestion occurs with generalized interstitial edema. Protein-containing edema fluid furnishes an excellent culture medium for the organisms ordinarily found in the mouth, and may lead to pneumonia. This outcome can sometimes be prevented by the administration of protein to control the edema, and by frequent turning of the patient. If the edema is on a cardiac basis, the heart failure must be treated with digitalis. Since penicillin is a relatively harmless drug, it is probably wise to begin immediate parenteral administration of 10,000 to 25,000 units every two to three hours to patients who exhibit the slightest pulmonary signs.

In most moderately severe cases functional damage to the liver can be demonstrated by bromsulfalein, hippuric acid, and other liver function studies, even before it is recognizable clinically. Damage to the liver may aggravate the disturbance of protein metabolism by preventing the formation of blood proteins, even though the dietary intake is adequate. The administration of amino acids orally or parenterally will not overcome this defect in formation. In an occasional case vitamin K has not been absorbed from the intestine, even though it was given orally in large amounts. An increase in the hemorrhagic character of the rash after compression of the veins of an extremity should cause one to suspect this condition. If the prothrombin time is found to be prolonged, 1 to 3 mg. of menadione should be administered parenterally. Unless the liver is damaged, this results in prompt return of the prothrombin time to normal. In one instance the additional administration of methionine, 1.5 to 3 Gm. daily, was necessary to help the damaged liver to form prothrombin. The administration of a high-protein diet from the beginning of therapy will help to protect the liver from damage. A repetition of the function tests during convalescence usually indicates that the damage is not permanent.

In many patients with Rocky Mountain spotted fever the kidney function, as measured by urea clearance tests, is decreased. In our experience the extent of kidney damage has not paralleled the clinical severity of the disease. Usually the amount of protein lost

through the damaged glomerular capillaries is not great and does not explain the precipitous and severe drop in serum proteins observed. Occasionally evidence of nephritis has been found. Persistent elevation of the nonprotein nitrogen during convalescence may be due not to renal damage, but to simple overloading of the kidney by the prolonged administration of a high-protein diet. In patients on a daily protein intake of 9.9 Gm. per kilogram of body weight, we have observed nonprotein nitrogen levels of 50 milligrams per 100 cc. on the same day that the urea clearance was 150 per cent of normal.<sup>11</sup> When the daily protein intake was reduced to 3 Gm. per kilogram and an adequate amount of fluids was administered orally, the nonprotein nitrogen has returned to normal. Repeated renal function studies during convalescence show little residual damage.

Most patients have some degree of encephalitis, evidenced by muscular twitching—which must be differentiated from that due to low blood chlorides or calcium—absent or abnormal reflexes, hiccup, or stupor. Occasionally the central nervous system involvement will be severe enough to cause death from respiratory paralysis. Severe headache, extreme restlessness, or increasing drowsiness due to an elevated spinal fluid pressure may be quickly improved by reducing the pressure half way to the normal level; the puncture should be repeated the following day, if necessary. If the optic disk margins are markedly blurred, cisternal puncture would be a safer procedure. If the stupor is deep, the patient may sleep with his eyes open; in this case, a mild sterile oil should be instilled two or three times a day to prevent the formation of corneal ulcers. Severe encephalitis may lead to permanent neurologic changes, such as alterations in personality, decreased mental ability, or persistent abnormal reflexes.

If the patient has no oral feedings, the danger of parotitis should be combated by swabbing the gums several times daily with the juice of half a lemon in an ounce of glycerine or mineral oil.

Gangrene may develop in the distal phalanx of an extremity as a result of complete thrombosis of an artery where no adequate collateral circulation is available. Necrosis of the skin may occur over the pressure points in comatose patients, or may develop in areas of severe hemorrhagic rash; meticulous nursing care, frequent turning of the patient, and the use of a rubber ring will partially avoid this.

#### ILLUSTRATIVE CASE

The following summary of the hospital record of an actual case of Rocky Mountain spotted fever illustrates the practical application of the principles dis-



cussed. The photographs in Figures 2 and 3 were made of this patient, and the data summarized in Figure 7 were taken from his chart.

A 14-year-old school-boy had been playing with dogs in the woods on his grandparents' farm. An engorged tick was removed from his left ankle 13 days before admission. Five days later malaise began, followed the next day by moderately severe headache, muscular tenderness, and fever. The local physician discovered pharyngitis, and prescribed a sulfonamide drug for 48 hours. When this proved ineffective, penicillin therapy was substituted without response. The temperature varied between 103° and 105.4° F. Six days after the symptoms began, a chill called attention to a fine macular rash on the forearms and legs, which spread to the trunk, but not the face. Aching and anorexia persisted, and the patient vomited on four occasions.

The sustained high fever began to subside by lysis and the rash to fade ten days after its appearance. Complications appeared early. On the 13th day,\* the boy was still critically ill. Rapid and dramatic recovery then began. By the 15th day, he was sitting up in bed, reading. He was discharged 24 days after the appearance of rash, weighing exactly what he did on admission.

**Physical Examination.** When the patient was admitted to the hospital three days after the rash appeared, the temperature was 104.2° F. (rectal), pulse 100, respiration 24, blood pressure 78 systolic and 50 diastolic. He appeared acutely ill, somnolent, and dehydrated, with cracked lips. Edema of the periorbital tissues, hands, and feet was present, in spite of the clinical evidence of dehydration. A faint, red, macular rash, which blanched slightly on pressure, was diffusely scattered over the entire body, except for the face, and was most prominent on the feet; the tourniquet test was markedly positive. The conjunctivae were injected. The lung fields were clear and the heart was not enlarged. A harsh systolic murmur was heard best in the third left interspace. The abdomen was slightly distended; a firm spleen was easily palpable three finger-breadths below the costal margin. Occasional purposeless muscular contractions were noted.

#### Laboratory Findings

**Diagnostic.** On the eighth day, agglutination of proteus OX19 was positive in a dilution of 1:20; complement fixation test was positive in a dilution of 1:3, which rose to 1:64 five weeks later.

**Therapeutic Control.** The hemoglobin was 11.5 Gm. on admission, 8.7 Gm. on the tenth day, and 14 Gm. after the fever subsided. The white blood cell count on admission was 6,600, with 63 per cent segmented and 14 per cent non-segmented polymorphonuclear cells; the highest count was 10,000 on the eighth day. The urine gave a 1 plus reaction for albumin on the day after admission but was negative thereafter. The cerebrospinal fluid pressure was 300 mm. of water, and the protein content was 365 mg. per 100 cc. Other laboratory findings are recorded in Figure 4.

#### Therapy

**Specific.** A skin test to Rocky Mountain spotted fever antiserum was negative 60 hours after the rash appeared; 30 cc. was given intravenously at once and 33 and 43 cc. by the same route on the fifth and sixth days, respectively. Little change was noted.

\*Hereafter the patient's course will be measured from the appearance of the rash.

Para-aminobenzoic acid was begun on the sixth day with an initial dose of 10 Gm., followed by 4 Gm. every two hours; an equal weight of NaHCO<sub>3</sub> was given with each dose. On the ninth day, the blood level rose to 50 mg. per 100 cc. The dose was reduced at once and the drug was discontinued 24 hours after clinical improvement was noted.

**Supportive.** A nasal Levine tube was passed on the day of admission, and the patient was fed 200 cc. of the milk formula every two hours. An average daily protein intake of 200 Gm., with a caloric content of 2,250 was attained. A slight diarrhea appeared, but subsided when belladonna was administered. By the 17th day, the patient took a soft diet, which was supplemented with between-meal feedings of the formula flavored with chocolate. Except on rare occasions, the total serum proteins were maintained above 5 Gm. per 100 cc. The transient azotemia and rise in blood pressure were attributed to functional overloading of the kidney.

The dehydration and hypochloremia present on admission were treated with glucose and saline intravenously. Additional salt up to 12 Gm. a day was given orally before the low level was corrected. With clinical recovery and subsidence of edema, the blood chloride rose to 110 milliequivalents per liter. Slight nausea disappeared when salt was discontinued.

On the fifth day the serum proteins were reported as 3.7 Gm. per 100 cc.; 25 Gm. of human albumin was administered. To raise a hemoglobin of 8.7 Gm. with as little increase in blood volume as possible, 250 cc. of settled red cells were given on the tenth day. For sedation 0.1 Gm. of sodium phenobarbital was given as necessary. Lumbar punctures on the seventh and eighth days improved respirations and reduced restlessness.

On the fifth day, oxygen therapy at six liters per minute was instituted for slight cyanosis and respiratory distress and continued ten days.

#### Complications

On admission peripheral circulatory collapse, with decrease in the circulating blood volume was present, as a result of water and salt loss. This was treated with crystalloids on admission, and the blood pressure rose to 90 systolic and 50 diastolic. On the fifth day impending circulatory failure, indicated by a drop in proteins and a rise in thiocyanate space, was treated with concentrated albumin. On the sixth day, gallop rhythm was heard; the venous pressure was 142 mm. of water, having risen from 114 on admission. To control the congestive heart failure, 0.6 Gm. of digitalis was given by tube, followed by 0.1 Gm. every three hours. Complete digitalization was achieved with 1.3 Gm. The electrocardiogram showed a PR interval of 0.24 second and digitalis effect; the gallop rhythm persisted until the 13th day. The total blood volume and interstitial fluid spaces remained high during this period. With clinical improvement and repair of the capillaries, edema disappeared and digitalis was stopped. Three weeks after discharge the PR interval was 0.20 second; the blood pressure 120 systolic and 80 diastolic; the only abnormal finding related to the heart was tachycardia.

The prothrombin time on the third day was 29.2 seconds, against a control of 18.1 seconds. The following day it increased to more than two minutes; thereafter 4 mg. of menadione was given parenterally every day. Beginning on the tenth day methionine was given orally in doses of

3.0 Gm. daily. On the next two days the prothrombin time rose again to more than two minutes. Some bright blood was passed by rectum for several days, and transfusions of fresh warm whole blood were given. On the 16th day the prothrombin time decreased and remained normal; the drugs were discontinued. Other liver functions, as measured by bromsulfalein excretion, galactose tolerance, and hippuric acid detoxification, were not impaired.

The patient complained of itching about the ankles 13 days after the initial dose of antiserum. Urticaria developed subsequently over the entire body, and transient arthralgia was evident. The slight increase in fever was attributed to serum sickness. Injections of adrenalin, 0.3 cc. of a 1:1,000 solution, and oral doses of benadryl, 10 mg. three times daily, alleviated the symptoms.

### SUMMARY

1. Rocky Mountain spotted fever is a severe generalized infection which markedly disturbs the functions of the entire body. The alterations result from the pathologic lesion—destruction of endothelium and necrosis of arterioles—and from changes in permeability of the capillaries.

2. The infecting agent, a rickettsia, can be attacked before the third day of rash by the administration of hyperimmune rabbit antiserum, and perhaps by para-aminobenzoic acid.

3. Supportive therapy should include from the beginning a high intake of all vitamins and a high-protein diet, supplemented with gavage feedings if necessary, to lessen the disturbance of protein metabolism, to protect the liver, and to prevent peripheral circulatory collapse. Selection of fluids and the mode of administration should be governed by careful laboratory control to anticipate complications and to insure the efficacy of therapy.

4. Preventive measures should include yearly administration of chick-egg vaccine before exposure, and inspection of the body and clothing twice daily while in tick-infested areas.

### BIBLIOGRAPHY

1. Wolbach, S. Burt: Studies on Rocky Mountain spotted fever, *J. Med. Research*, 41:1-197 (Nov.) 1919.

2. E. Dyer, and A. Rumreich: An infection in Rocky Mountain spotted fever type, *U. S. Public Health Rep.*, 46:463-480 (Feb. 27) 1931.

3. Ricketts, H. T.: A micro-organism which apparently has a specific relationship to Rocky Mountain spotted fever, *J. A. M. A.*, 52:379-380 (Jan. 30) 1909.

4. Parker, R. R.: Rocky Mountain spotted fever, *J. A. M. A.*, 110:1185-1188 (Apr. 9) 1938.

5. Topping, Norman H.: Rocky Mountain spotted fever. A note on some aspects of its epidemiology, *U. S. Pub. Health Rep.*, 56:1699-1703 (Aug. 22) 1941.

6. Cox, Herald R.: Rocky Mountain spotted fever. Protective value for guinea pigs of vaccine prepared from rickettsiae cultivated in embryonic chick tissues, *U. S. Pub. Health Rep.*, 54:1070-1077 (June 16) 1939.

7. Baker, George E.: Rocky Mountain spotted fever: diagnosis of the disease, *Rocky Mountain Med. J.*, 41:466-478 (July) 1944.

8. Virus and Rickettsial Diseases. A symposium held at the Harvard School of Public Health. Cambridge, Mass., Harvard University Press, 1943.

9. Bengtson, Ida A., and Norman H. Topping: Complement-fixation in rickettsial diseases, *Am. J. Pub. Health*, 32:48-58 (Jan.) 1942.

10. Harrell, George T., William Venning, and William A. Wolff: The treatment of Rocky Mountain spotted fever with particular reference to intravenous fluids, *J. A. M. A.*, 126:929-934 (Dec. 9) 1944.

11. Harrell, George T., William A. Wolff, William L. Venning, and John B. Reinhart: The prevention and control of disturbances of protein metabolism in Rocky Mountain spotted fever, *South. Med. J.*, 39:551-558 (July) 1946.

12. Topping, Norman H.: Rocky Mountain spotted fever. Further experience in the therapeutic use of immune rabbit serum, *U. S. Pub. Health Rep.*, 58:757-775 (May 14) 1943.

13. Topping, Norman H.: Experimental Rocky Mountain spotted fever and endemic typhus treated with pron-tosil or sulfapyridine, *U. S. Pub. Health Rep.*, 54:1143-1147 (June 30) 1939.

14. Rose, Harry M., Richard B. Duane, and Edward E. Fischel: The treatment of spotted fever with para-aminobenzoic acid, *J. A. M. A.*, 129:1160-1161 (Dec. 22) 1945.

### Hodgkin's Disease

In an effort to learn more about the etiology and treatment of Hodgkin's disease, the Hodgkin's Disease Research Foundation has been recently organized. Dr. Herman A. Hoster, director of cancer research at Ohio State University, has been made president of the foundation. The scientists affiliated with the group seek to raise \$2,000,000 this year to sustain a broad program of laboratory and clinical research on the disease which attacks most frequently persons between

20 and 40 years old and levies an annual death toll of 3,000. Though Hodgkin's disease bears many similarities to cancer, the finding of inclusion bodies in affected tissue has suggested that a virus may be the causative agent. If this turns out to be the case, the development of an effective vaccine is a hopeful possibility. A well organized research program may provide the answers.

# Differential Diagnosis and Symptomatic Treatment in the Asthmatic Patient

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No physical examination of an asthmatic patient should be considered complete unless there has been an accurate examination of the nose and throat and of the paranasal sinuses. Correct diagnosis necessitates the use of the nasopharyngoscope and x-ray of the sinuses. It is an interesting fact that very occasionally sinuses may transilluminate fairly well, and yet have a considerable degree of pathology. The pathologic changes one sees in these sinuses are different from those of acute purulent sinusitis seen in the nonasthmatic. In the asthmatic they are the results of chronic infection manifested as thickened polypoid tissue, and called hyperplastic sinusitis.

In the child, it is essential that infected foci be removed and that recurrent tonsillar and adenoid tissue is not present. Fully 50 per cent of the patients who have had previous tonsillectomies and adenoidectomies have had a recurrence of tonsillar and adenoidal tissue. The use of soft-tissue x-rays to outline the nasopharynx is of the greatest importance in children in determining the presence and size of adenoid tissue. Where it is localized in one mass, surgical removal should be done. Where it is disseminated, the use of radium or x-ray therapy is indicated and excellent results are reported in these cases. The examination of the chest should never be considered complete without x-rays. The clinical signs during an asthmatic attack, sonorous râles and the like, are too well known to require much time in discussing them. Examination of the thorax, however, is extremely important. Marked emphysematous changes are indicative of a chronic process in the lung which frequently has come to the stage of irreversibility. It is likewise important to perform a vital-capacity determination, although it must be borne in mind that, during an asthmatic seizure, there may be a reduction in vital capacity which subsequently corrects itself. The old bromide that "all that wheezes is not asthma" is borne out in the clinical experience of those of us who have seen this condition over a period of years.

In the differential diagnosis, the most frequent condition from which it must be distinguished, particu-

larly in the child, is the so-called asthmatic bronchitis. I object to this term for the reason that it is highly misleading. Most parents are given a reassuring prognosis with the statement that the child will outgrow the asthmatic bronchitis. The opinion that a child or an adult will outgrow his asthma should never be given and it is the worst possible sort of advice, for the reason that the allergic diathesis is a constitutional defect and the clinical syndrome depends entirely on the contact and precipitating causes. It is much wiser to consider each case of asthmatic bronchitis as a potential asthmatic until proved otherwise and, for this reason, to do screening tests with some of the important inhalants and foods to determine whether or not the patient is allergic. We frequently determine this fact in one diagnostic visit. Complete testing should by no means be considered necessary to place the individual, whether he be child or adult, in the proper group. The reason for my insistence on this point of view lies in the fact that too often the diagnosis of asthmatic bronchitis is made with the assurance that all will be well; then that kind prognosis is rudely upset by a severe attack of asthma.

Pertussis can frequently present a very difficult differential diagnosis in the young child. There is, however, one fairly good clinical aid, namely, the appearance of a high degree of lymphocytosis in the blood picture.

Transitory bronchial pneumonia is frequently seen, both in the child and in the adult, and is characterized by marked febrile response and an increase in respiratory rate, usually improving, particularly in children, after a period of 24 hours. The administration of small doses of epinephrine often help differentiate this condition.

Bronchitis is characterized by a persistent temperature and a leukocytosis and by the absence of an expiratory dyspnea.

Foreign bodies are particularly important and are very difficult to detect if the foreign body is radio-lucent in character, like a nut or cartilage. One of the most important clinical signs is a persistent, brassy

cough with or without wheezing. The diagnosis depends for confirmation on a bronchoscopic examination.

Tumors of the lung depend for their symptomatology entirely on their location. Mediastinal tumors produce the symptoms of asthma by compression. Carcinoma of the lung is characterized, often in its earliest stage, by a severe degree of dyspnea, which is, however, not expiratory in character. In operative cases, where primary tumors have been removed, metastatic involvement of the lung occasionally produces asthmatic symptoms. The diagnosis, of course, depends on x-ray examination.

Tuberculosis in children is apt to be miliary in character, but it is not too uncommon to see pulmonary tuberculosis as a concomitant in allergy. The incidence of tuberculosis, however, is not any higher in the asthmatic than it is in the normal. One error that is frequently made is a tendency to diagnose hilar tuberculosis in the asthmatic patient as a result of his having increased hilar shadows on x-ray. This error should not be made, as the increase in the hilar markings is due entirely to absorption from a chronic focus of infection in the upper respiratory tract or the sinuses.

Atelectasis is seen fairly often as a result of the plugging of the bronchial tubes with tenacious mucus. This presence of tenacious mucus is one of the most characteristic findings at autopsy of an asthmatic patient. It is best relieved by bronchoscopy or, in children, by the administration of syrup of ipecac.

Bronchiectasis is relatively uncommon but whenever suspected, a contrast medium should be instilled into the lung to rule it out. The incidence of sacular bronchiectasis in asthmatics is quite small.

The Loeffler syndrome may be seen, particularly in children, in whom the x-ray shows numerous areas of consolidation which are temporary in character. It is accompanied by a low-grade fever and a very high blood eosinophilia, up to 60 per cent. The exact character of these lesions is unknown. Eosinophilia of such intensity is indicative of periarteritis nodosum or Loeffler syndrome.

Cardiac asthma likewise gives asthmatic symptoms which are very prone to come on suddenly at night. They are an expression of left-sided failure usually, and in those cases where it is marked, it is an indication of cardiac failure and decompensation. The picture of cor pulmonale is occasionally seen and is accompanied by a right-axis deviation in the electrocardiogram with right-sided heart failure. The treatment, of course, in this group is directed toward the cardiac failure. An interesting point about electro-

cardiograms in the asthmatic is the fact that they may completely reverse themselves when the patient becomes asymptomatic, if the degree of damage is not too extensive. Where this reversibility does not occur, the prognosis is more grave. There is, however, no definite pattern in the electrocardiogram which is characteristic of all asthmatics.

#### TREATMENT OF A MILD ATTACK OF ASTHMA

The mild attack of asthma is relatively easy to control, both in children and in adults, by the use of ephedrine in combination with aminophylline or, in children, in the form of a syrup of ephedrine, N. F. Epinephrine in a 1 to 100 dilution used as a spray to be inhaled orally is likewise very effective. The use of expectorants, both ammonium chloride and iodides, is of great value. In these patients, where persistent, unproductive cough is the outstanding symptom, the use of syrup of ipecac to the point of producing emesis is of great value.

#### TREATMENT OF STATUS ASTHMATICUS

Status asthmaticus in children differs markedly from status asthmaticus in adults in that the duration is much shorter in children. In both children and adults the history is usually one of upper respiratory infection which terminates in severe asthma. The treatment consists of: 1. The use of oxygen, either by nasal catheter or placing the patient in an oxygen tent if there is cyanosis. This tends to improve the patient's dyspnea. 2. An enema is immediately given to reduce abdominal distension and is best followed in the adult patient by the use of two compound cathartic pills followed the next morning by a ½ ounce dose of magnesium sulfate and another high enema. 3. In cases with a high fever, x-ray of the chest is indicated to rule out the possibility of pneumonia. 4. Sedation in children is accomplished by the use of codeine in the form of a suppository containing ½ to 1 grain. In the adult, various sedatives can be used—morphine, however, should never be used as it depresses the respiratory center and there are many reports of patients dying after its use. Demorol, in the dosage of 50 or 100 mg., is quite effective in many of these cases. Counterirritation in the form of mustard plasters, in a patient not sensitive to mustard, is to be encouraged. 5. A diet of fruit juices and fluids for the first 24 to 36 hours should be given, and care must be taken to observe the food intake and sugar supply.

Epinephrine in oil, if effective, should be used. Unfortunately, most of these patients are epinephrine fast and use of aminophylline intravenously is indi-

cated. In children, aminophylline is best used in the form of a rectal suppository containing 2 to 3 grains. In the presence of any pulmonary infection, the use of sulfadiazine or penicillin is indicated. The use of penicillin aerosol has received great publicity. Its value, however, lies largely in the treatment of the acute infective process involving the bronchial tubes. It has not, in my experience, proved to be of any value in the treatment of hyperplastic sinusitis, or in the treatment of asthma. Penicillin, parenterally, like-

wise has not proved to be of any great value in cases of asthma.

Using these measures, I have never seen a child die of asthma. However, occasionally in the adult, despite all efforts, death may occur and it is therefore imperative that these patients be properly diagnosed and treated in order to avoid the occurrence of a status asthmaticus.

30 West 59th Street

### The B.M.J. Meets the Crisis

What the blitz of 1940 was unable to do, the English fuel crisis of 1947 has accomplished. The British Medical Journal which published throughout the war in spite of bombings and shortages of paper and labor has been reduced in the issues of February 22 and March 1 to a single mimeographed sheet completely covered on both sides with the "news and views evaporated to dryness." Their printers having been refused permission to use electricity, the issues were run off on a hand-operated duplicator by the Secretary of the British Medical Association. The issue was addressed to the 62,000 subscribers by an addressing machine using foot power instead of electricity. The editors and the whole staff are to be congratulated on their initiative and resourcefulness. The B.M.J. and one or two lay publications were the only members of the weekly press that avoided suspension of publication for the two-week period of acute coal shortage.

The smallest issue since 1840 still had room to give the key points of letters received, including a diary of events of interest to doctors, sections on news, epidemiology, questions and answers and advertisements of vacancies.

The editor hoped that the abbreviations would prove unambiguous. The following excerpts are from the February 22 issue.

**COAL AND MEDICINE.** Shivering, we tend to think of coal only as fuel. Coal is Medicine as well. RUNGE discovered in 1834 carbolic acid, a coal-tar product. With carbolic LISTER stoked the fires of surgery for posterity. PERKIN'S discovery of the aniline dye mauve in 1856 was the starting point of modern medicine. WEIGERT in 1871 stained bacteria with the aniline dyes of coal-tar, and KOCH soon followed suit. EHRLICH hit upon the idea that certain cells had chemical affinity for certain dyes. This led to differential staining of tissues and the birth of chemotherapy. The red dye-stuff prontosil, patented in 1932, began a revolution in medical treatment—with the sulpha drugs. The malarial remedies mepacrine and paludrine depend for synthesis on coal-tar distillates. From

naphthalene comes the synthetic analogue of vitamin K. Phenol is the chemical parent of a common purgative, of aspirin, and of the synthetic oestrogen stilboestrol. Coal gives doctors their most potent remedies and research workers essential chemical instruments. And if nylon that comes from coal is wanted by colliers' wives for stockings the surgeon also wants it for his sutures.

**POINTS FROM LETTERS.** C. A. WELLS says pentothal-curare anaesthesia gives agreeable induction, complete relaxation, a quiet field, and rapid recovery; G. S. A. KNOWLES urges use of prostigmin at end of operation to combat apnoea; J. MONTGOMERIE finds hyoscine HBr. 1/100 gr. (0.65 mg.) prevents excessive salivation on recovery from curare. H. W. BARBER, surprised that our leader (Jan. 18, p. 96) mentions endocrine receptors as new conception, quotes B. BLOCH (*Brit. J. Derm. Syph.*, 1931, 43, 61). D. A. LONG believes stomatitis caused by penicillin plus sucrose base, prefers viscous base pastille.

**DAIRY.**—R. C. S. Feb. 24–28, 3.45 & 5.0, lects. anat., physiol., path. R. Inst. P. Hlth. Hyg., Feb. 26, 3.30, J. N. Agate: Trmt. Com. Indust. Dis. Med. Soc. Lond., Feb. 24, 9 p.m., E. Finch: Exptl. Cancer. Med. Soc. Vener. Dis., Feb. 22, 2.30, R. Thomson: W. R. Problem Cases. Lond. Sch. Derm., Feb. 25, 5.0, R. T. Brain: Com. Skin Affect. Childh., etc.

**NEWS.** (1) Hunterian Soc. and R. C. S. celebrated John Hunter's birthday on Feb. 13 and 14. The Duke of Gloucester, the Soviet Ambassador, and the Earl of Athlone attended R. C. S. dinner. Mr. Attlee said aim of N. H. S. Act was to provide for all skill and facilities formerly confined to a few. President R. C. S. believed if plan had flaws British sense and Parliamentary wisdom would remove them. (2) Editor J. A. M. A. (Jan. 11) writing centennial history says GROSS 1874 claimed Columbus took Syphilis from Old to New World, not *vice versa*. (3) Advt. B. M. J. Feb. 1, wrongly stated price London Aberdonian's dinner (18s.) included wines. Aberdonian Secy alarmed at mistake and demands for tickets. (4) Doctor's certificate needed for electricity in banned hours.

**ADVT. VACANCIES—CANDIDATES SHOULD APPLY TO ADVERTISER.** M. O. H. & S. M. O. Leeds: A. M. O. Nottingham, Dumbarton: R. M. O. (B. 1) Plymouth, S. Shields: M. O. O. (B. 1) Beverly E. H. East Riding: D. M. O. H. & D. S. M. O. Wakefield: A. C. M. O. H. West Suffolk C. C.: A. M. O. H. & A. S. M. O.

# Cases from the Medical Grand Rounds Massachusetts General Hospital

Edited by LEWIS K. DAHL, M.D.

BOSTON, MASSACHUSETTS

## CASE 10

### ESOPHAGEAL VARICES

DR. WALTER BAUER: This morning we would like to present a patient, Mr. B., aged 65, who comes in because of hematemesis. His disease is not an uncommon one in the medical wards of a hospital like this. From the evidence at hand it would appear that we are dealing with an individual who is suffering from portal hypertension and that the hematemesis is the end result of one of the complications seen in people with portal hypertension. We would like to present him this morning with the hope that Drs. Jones and Volwiler will tell us something about the success in treating this particular complication in the past and what the newer procedures employed elsewhere and being used here, may have to offer a patient of this sort.

DR. GEORGE MELLINGER: Mr. B., No. 554960, has been remarkably free of symptoms until the present illness, although he did complain of a vague dyspepsia of five years' duration. This apparently came on after meals, especially after eating too much, was very mild in character and was not in the form of pain or severe discomfort. It was rather intermittent, the last episode having occurred about two months before the present admission. This episode was also associated with a dull, nonradiating pain in the right costal margin posteriorly. About 45 minutes before admission on November 24, 1946, while the patient was taking a hot bath, he suddenly noticed the onset of dizziness, weakness, and he began to sweat. He got out of the bath and almost immediately had severe nausea and vomited about one or two pints of bright red blood. At the same time, he passed some bright red blood by rectum. Because of this, his wife called his local doctor, who immediately referred him to this hospital.

The past history had been remarkably negative. He had very little disease, measles and mumps being about the only diseases. The history in respect to alcohol was almost negative. The patient repeatedly says that he has never drunk much alcohol. The maximum, he says, is about one to two drinks a week,

never more. The diet, according to the history, has always been adequate. He has never gone on a diet, never been a dietary fadist, has always had plenty of meats, vegetables, and fruits. He has never been exposed to any industrial or other liver toxins that we could discover.

On admission to the Emergency Ward, the patient was obviously in shock. The blood pressure was 70/40 and he was very pale and weak but not sweating. The pulse was 72; slow considering the blood pressure. Because of the blood pressure, 400 cc. of normal saline followed by 500 cc. plasma were given intravenously while waiting typing and cross-matching of blood. He was then given 1,000 cc. of whole blood.

The rest of the physical examination showed several dilated blood vessels on the nose. The heart and lungs were normal. The abdomen was somewhat distended, but no fluid or shifting dullness was made out. The liver was palpated at the costal margin, but the upper margin was in the sixth interspace, so the liver was small. The spleen was about three to four fingers below the costal margin on deep inspiration. The rest of the physical examination was essentially negative. After the patient received the blood his blood pressure was 105/60.

(Patient brought in.) This is Mr. B. The only positive physical findings which we can demonstrate at the present time are the telangiectasia on the nose, which I mentioned, and the physical findings in the abdomen.

DR. CHESTER M. JONES: This is a remarkably accurate picture of the liver. The liver edge can be palpated at the end of inspiration, that being the costal margin. The liver is obviously normal or small; rather than large.

Dr. Bauer, may I object to one statement? Those are not telangiectasia; but just dilated vessels. It is quite important to state that because a true spider angioma or telangiectasia that you get in this disease is practically pathognomonic. This gentleman does not have it.

DR. MELLINGER: Laboratory studies reveal the urine to be normal; the hemoglobin by copper sulphate

method when he was first admitted was about 16 Gm., but after plasma was given it was 9 Gm. I rather suspect that the second determination was accurate. The white count was 10,600 with 93 per cent polymorphonuclears; the stool showed gross red blood with a four plus guaiac test.

Chemical studies showed a total serum protein of 6 Gm.; albumin 4.04; globulin 1.94; cephalin flocculation one plus at the end of 24 and 48 hours, both; and the bromsulfalein (B.S.P.) test showed 34 per cent retention of the dye in the serum at the end of 45 minutes.

Gastro-intestinal x-ray series taken on the first day after admission showed the characteristic picture of esophageal varices, which I hope Dr. Schatzki will discuss shortly.

TABLE 1

*Results of Chemical Studies*

	TOTAL PROTEIN	ALBUMIN	GLOBU- LIN	CEPHALIN FLOCCU- LATION	B.S.P. TEST
11/27/46	6.00 Gm.	4.04 Gm.	1.96 Gm.	1+	34%
12/4	5.82	3.36	2.46	Neg.	
12/6	5.72	3.82	1.90	Neg.	12
12/9	6.25	2.84	3.41	1+	6
12/13	6.57	3.99	2.58	Neg.	8
12/17	6.42	4.15	2.27	1+	14

I have charted his chemical finding on the board (Table 1). The total protein shows approximately the same level throughout. The albumin also shows approximately the same level. The globulin shows a slight rise during his hospital course. At one point the albumin-globulin ratio was reversed, but we doubted the significance of this since two days previously it had been normal. The B.S.P. shows a sudden return toward normal: The first day, 34 per cent retention; a return to 6 per cent on the 13th day; and one several days ago 8 per cent. The cephalin flocculation has always been within normal limits. The blood hemoglobin has remained about 9 or 10 Gm. The stool guaiac test has been consistently four plus up until yesterday when it was three plus. The stools have become more normal. The patient has been treated only with a high vitamin, high calory, high protein, low fat diet, and bed rest. We called in the various groups for consultation and it was decided that this man should probably have a spleno-renal anastomosis and he is being prepared for that operation. I hope he will have that and other treatment discussed at this time.

DR. BAUER: Dr. Schatzki, do you have anything to say?

DR. RICHARD SCHATZKI: It is one of those instances where the patient was being examined for the cause



FIG. 1. Esophageal varices.

of hemorrhage and the first x-ray showed the story. You can see those tortuous, markedly dilated veins in the lower end of the esophagus (Fig. 1).

DR. JONES: How many days after admission were the x-rays taken?

DR. BAUER: The first day. The hematemesis experienced by this patient was due to rupture of an esophageal varix. Esophageal varices, a manifestation of portal hypertension, are no longer a matter of diagnostic conjecture. In recent years our radiologists have demonstrated their presence with increasing frequency, thereby establishing the cause of the hematemesis with reasonable regularity in cases of this type.

The liver tests employed have revealed very little evidence of hepatic insufficiency. The greatest retention of B.S.P. was observed a day or two after entrance. When the test was repeated a few days ago only six per cent of the dye was retained. The former finding probably indicated temporary hepatic insufficiency caused by the massive blood loss and ensuing shock. Do you agree with this interpretation, Dr. Jones?

Following the initial transfusions the erythrocyte count has remained at approximately two and a half million. His condition having remained good, we

deferred additional transfusions until there was no further evidence of bleeding. He will, however, receive whole blood transfusions prior to undergoing any surgical procedure.

We are now confronted with the problem of treating esophageal varices in a man with cirrhosis of liver which appears to be reasonably well compensated. To date their treatment has been unsatisfactory. Recurrent hemorrhage is the rule, although I have seen several patients go as long as ten years without a recurrence. Recently venous anastomosis has been advocated on the assumption that shunting the blood will lessen the load carried by the esophageal varices, thus reducing the likelihood of future hemorrhage. I have asked Dr. Jones and Dr. Volwiler to discuss the results to date of surgical procedures of this type.

DR. JONES: I think this case represents a good example of compensated cirrhosis where the significance of the underlying disease would have been missed if the patient hadn't bled. Furthermore, it is not too infrequent for us to see patients with cirrhosis of the liver where the diagnosis is obvious and where nobody bothers to look for esophageal varices by x-ray. That has happened recently in several cases that I have seen. The detection of esophageal varices is one of the few measures that indicates prognosis. Most of our tests do not give us any absolute prognostic information. When you demonstrate varices you not only demonstrate the existence of portal hypertension, due to one cause or another, but also you expect that most of these patients are going to die from hemorrhage regardless of how well compensated the liver is. Dr. Bauer has said that an occasional patient goes ten years after an initial hemorrhage, and that is true. I assume there are cases on record even longer than that, but by and large, once a patient with varices has had an excessive hemorrhage then we should expect further hemorrhages until a fatal one ensues. This is so serious that again and again efforts have been made to determine some sort of method whereby the degree of portal hypertension referred to the esophageal veins can be diminished or reversed. The degree of portal hypertension is very real, and Dr. Linton, for instance, has measured in quite a few patients the amount of pressure of the portal system under these conditions. Whereas normally it is about eight to ten or twelve cm. of water or saline, you may see it as high as 50 or 60 or 70 cm. in those cases with portal hypertension. It shows the cause of the esophageal varices and one reason why they tend to bleed profusely.

A second point is that with this venous bleeding, treatment should be different from that employed in

patients bleeding from an ulcer, gastritis, or diaphragmatic hernia. In gastritis the bleeding is usually of capillary origin and in an ulcer the bleeding is arterial. If there is an elastic media the artery will contract, the bleeding will stop, and you can feed your patient. In the present instance, you are dealing with hemorrhage from veins which have little or no contractility. I think feeding is contraindicated during the acute phase of bleeding.

This patient was x-rayed 24 hours after he came in, or about 24 hours after hemorrhage had occurred. Such a procedure, I think, is a very important diagnostic measure. It is not done in some cases but usually we should elucidate the diagnosis, and be able to say that the bleeding is due to ulcer or cancer or varices, or to spot the lesion so that the surgeon can be ready for emergency measures. We had a patient 80 years old recently who had a massive hemorrhage. We took x-rays, although he was pretty shaky and found a penetrating gastric lesion. This was operated on successfully during the bleeding episode, simply because we knew where to go.

I am sure Dr. Bauer is right about this patient. He is a highly compensated "cirrhotic," whose liver function is very good; but, subjected to the massive hemorrhage and shock as he undoubtedly was, for the time being one of the liver functions (bromsulfalein excretion) was seriously interfered with as a temporary matter, and subsequently came back to a level which for him is about normal—10 to 15 per cent retention.

Now, as to the surgical measures to prevent a future hemorrhage from his varices. Once they are demonstrated, we still don't know when to interfere. I think we all feel very ignorant on this particular point. Should we operate on varices that only involve the lower third of the esophagus before hemorrhage? Should we wait until they bleed? Should we operate more quickly when they involve the lower half? Or should we operate immediately when the varices involve the entire esophagus? That is something we are trying to find out. What does the appearance and size and location of varices mean prognostically? How much time do you have? Splenectomy has been almost a complete failure in the patients with cirrhosis and esophageal varices. I mean by that that it has not apparently done any more than just postpone the evil day. It does remove a large amount of the blood supply that comes into the portal system but esophageal bleeding still takes place, because the cause, the portal hypertension is still there, and it can be transmitted through other collaterals. Tying all the coronary veins of the stomach has been attempted. Sclerosis of the esophageal



varices by injection of sclerosing solutions has been undertaken. It may have reduced the bleeding but it has not stopped the danger of future bleeding, and it is at best a palliative procedure and dangerous. Ligation of all the veins in sight has been fruitless. The first highly original measure that has been devised is the measure that Dr. Blakemore of New York has outlined. Dr. Volwiler will tell you about it, but it means shunting of the portal stream into the systemic circulation by the left renal vein. That is what we propose to do here. It is undoubtedly true that this can be done. The question is when to do it. We are still floundering, I think, as to the exact and proper time. In this case I think there is very little doubt that when this man gets back on his feet or nearly so, you must go in on the crest of his improvement, possibly on the crest of one of these transfusions, and attempt this anastomosis, hoping it is anatomically possible. The success of this operation, I believe, will depend on the ability of the sick liver to stand a long, hard operation: splenectomy, dissection of the splenic vein, dissection of the left kidney from its bed, freeing of the left renal vein and finally a splenorenal anastomosis. That is a long, hard operation. Unless the liver is pretty good, it can't take it. There are none of our function tests which give information as to how much it can take. But this patient will start with a good balance in his favor, I think, and from the experience we have had already I would guess he stood a very good chance of being able to complete the operation.

Dr. Volwiler has some figures.

DR. PAUL D. WHITE: How about portal-caval anastomosis?

DR. JONES: I would be against that. The experience they have had in New York suggests that their results with this procedure have not been as successful as they hoped. Actually you are performing an Eck fistula, and that may damage the liver. In doing an Eck fistula you divert a lot of your hepatic blood supply into the systemic circulation and do not help the liver by so doing. I think they are beginning to get that impression in New York. If you could divert it into the renal vein you would probably be much wiser.

DR. WHITE: Could you get a smaller flow then?

DR. JONES: That is right. You cut off the head of pressure. It is much more difficult and dangerous in most instances.

DR. WADE VOLWILER: This is obviously a mechanical problem, and a mechanical problem requires a mechanical solution. In the history of the attempts to remedy this process we have met with pretty complete failure up to date, up to the advent of the

maneuver suggested for this operation. Splenectomy as Dr. Jones said, has always been a failure, although it removes approximately 40 per cent of the inflow of the venous blood to the portal system. In summing up the statistics of this procedure for the relief of portal hypertension in 1942, Pemberton of the Mayo Clinic reporting on 226 patients, showed that after five years only 55 per cent were still living and more than 50 per cent who were alive had had recurrent hemorrhage. Omentopexy has met with failure. Ligation of the para-esophageal veins and the coronary veins below the diaphragm has been futile. Injecting the esophageal veins with a sclerosing solution alone is analogous to the therapy of varicose veins in the leg with sclerosing injections only. As long as the mechanical problem is present it is of temporary benefit or of no benefit.

We are interested now in the formation of an artificial shunt from the portal system to the peripheral venous system to solve this problem mechanically.

The original maneuver that was suggested is not a new idea. It was attempted in the 19th century but because of the surgical technic it was impossible to pursue it adequately. Dr. Blakemore in New York is responsible for revival of the idea and for the successful operative technic. Originally when it was devised, the left kidney and the spleen were both removed and an end-to-end anastomosis performed over a vitallium tube between the splenic and left renal veins. Now it has been found that removal of the left kidney is not necessary. One can do an end-to-side anastomosis retaining the left kidney. Dr. Blakemore has demonstrated that end-to-side anasto-

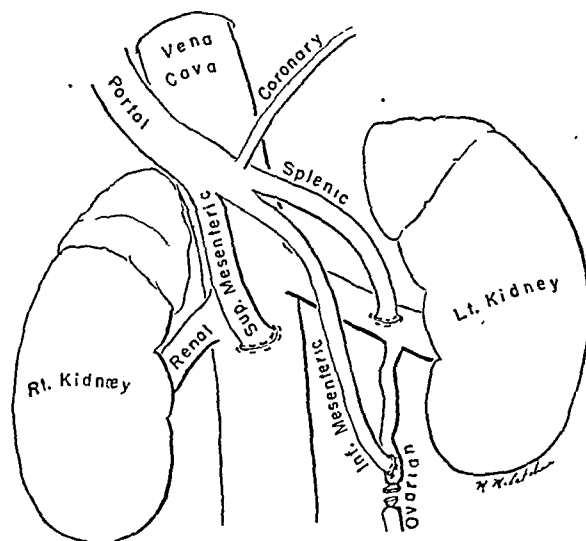


FIG. 2. Diagram illustrating various anastomoses used: (1) Splenorenal, end-to-side; (2) superior mesenteric to inferior vena cava; (3) inferior mesenteric to left ovarian. (Courtesy of Dr. Robert Linton.)

moses are more likely to remain patent than end-to-end hookups. Removal of the spleen alone reduces by 40 per cent the inflow of blood to the portal circuit. There is a considerable argument as to whether the use of the vitallium tube is necessary. Dr. Linton does a very careful suture technic without the use of the vitallium tube which seems to work very well.

One obviously would like to have as large an anastomosis as possible to decompress the portal circuit. The splenorenal, although it helps, is perhaps not as large an opening as one would like to have, and because of that there was a certain popularity in New York for a direct Eck fistula between the main portal vein and the inferior vena cava to provide a larger opening. In doing so, one severs completely the portal supply of blood to the liver. We know that this is unsound, and the physiologists and internists were very skeptical when these patients with cirrhosis were first subjected to that procedure. It is technically a very difficult operation but a certain number have been done, and the physiologists are much gratified to learn that after ten or twelve months some of these patients with cirrhosis are beginning to have episodes which may be interpreted as attacks of cholemia.

The site of the portal obstruction often may not be determined until laparotomy, and the anastomotic procedure to be done depends upon the location of the obstruction. One can do an end-to-side splenorenal anastomosis, which is probably best adapted to those patients if splenectomy has been previously accomplished; one can anastomose the left ovarian vein to the inferior mesenteric or the superior mesenteric to the inferior vena cava. All these maneuvers have been done by Dr. Linton in operations here for portal hypertension. We have done ten operations in this hospital, the first of which was accomplished by Dr. Richard Sweet in March 1944; the others have been done by Dr. Linton. Often histologic material may help one decide upon the timing of the operation, and may indicate a short preoperation delay to better improve liver function by intensive medical treatment.

Now what about statistics for the operation to date? The longest patient has gone only three or four years in New York. Our first case was done in March 1945. It is much too early to draw definite conclusions as to the results of the procedure. In New York, reporting on his cases up to last February, Blakemore had 14 patients with two operative deaths. About an equal number of spleno-renal anastomoses and Eck fistulas had been done. We have had ten cases in which five have been cirrhotics. We have had 40 per cent mortality in our experience, but let us examine the cases. All the deaths have been in those with cirrhosis. Except for one patient these have been the worst possible

operative risks that one could wish for. Two were very far advanced cirrhotics. One had a mousy odor. Two of them were repeatedly having massive hemorrhage from their esophageal circuit, and the operation was done as a last desperate measure with the hope that one might avoid a fatal outcome, which is the wrong time to perform it. Certainly if it is often done at that time the operation will receive a very bad reputation as to operative risk. One patient died not of operation, but from a transfusion reaction. We have today only one operated cirrhotic who has survived; 18 months afterwards she is doing very well. By laboratory tests her liver function shows an improvement rather than a deterioration, which has been the general experience in New York.

DR. WHITE: Dr. Volwiler, do you assume or find that cases of cirrhosis without important esophageal varices have developed an adequate collateral circulation? Or do you think you cannot make a statement about that.

DR. VOLWILER: I don't know the answer to that.

DR. JONES: Doesn't that depend on the amount of fibrosis?

DR. WHITE: I notice some of your collaterals went into the renal vein.

DR. VOLWILER: I think ordinarily when the collateral circulation has developed, there is a well developed supply into the esophageal circuit as a rule, but when one sees varying masses of fibers in cirrhosis a portal hypertension may be quite variable.

#### *Editor's Note*

On the 11th of January 1947 a left splenorenal vein anastomosis was performed as well as a splenectomy. Immediately following the operation he bled profusely from what were assumed to be esophageal varices and he required seven transfusions in addition to the nine given during the operation. On the 15th of January he had another bout of hemorrhage, requiring a total of three pints of blood before his condition was normal again. Thereafter his course was essentially uncomplicated and unremarkable, and he was discharged on a six-meal bland diet on the 1st of February. No further follow-up data are available at the present time.

#### CASE 11

##### ?CONSTRICTIVE PERICARDITIS

DR. PAUL D. WHITE: This case is a diagnostic problem, which on entrance I thought was quite easy. I was inclined to call the case a classical one, but because of the very striking and rapid improvement, I must say I am a little doubtful now. I have not

switched to other diagnoses which, however, are possible. Mr. C. will be discussed by Dr. Donald.

DR. JAMES H. DONALD: Joseph C., No. 181315, is a 43-year-old fish cutter who entered this hospital on December 27, 1946 by way of the Emergency Ward with the chief complaint of swelling of the abdomen for one week. His admission diagnosis was cirrhosis. For about one year the patient had noted some dyspnea on exertion, but was never incapacitated. For about three or four months he had had intermittent episodes of massive swelling of the abdomen, face and neck. These were accompanied by decrease in urinary output but otherwise no subjective sensation. With the reappearance of spontaneous diuresis, the swelling would decrease. He had continued work until one week before coming to the hospital, when again the swelling appeared, this time continued longer and, with the accompanying dyspnea, finally prevented him from working.

His past history was essentially noncontributory, being negative for symptoms of the agents commonly causing edema. His past history showed a strongly positive history of contact with tuberculosis. He also had had moderate alcoholic intake for at least 15 years, amounting to three whiskies with ale chasers each day. He had had "shakes" but never frank delirium tremens, and had never missed work.

Physical examination on admission revealed an obese, markedly edematous man in great distress and appearing acutely ill. He was breathing with loud and groaning noises. His pulse was 140, blood pressure 140/110, respirations 20. The edema was most pronounced in the head and neck. There was massive ascites. It was felt by the initial examiner that a fluid wave and shifting dullness were unequivocal. The examination of the lungs through an obese and edematous chest wall revealed nothing. The heart was enlarged to 9.5 cm. to the left of the midsternal line. The rate was 140, regular, and no murmurs were heard. The initial examiner believed that the pulse was not paradoxical in character. There was slight ankle edema, markedly out of proportion to the edema of the upper portion of the body.

Shortly after admission an electrocardiogram was made. It showed auricular flutter with a 2:1 block, with a ventricular rate of 140. Shortly after admission the venous pressure was 355 mm. H<sub>2</sub>O and a decholin circulation time was 30 sec. (normal 13-16 sec.). He was treated by rapid digitalization, diuretics, both ammonium chloride and mercurials.

His admission urine contained two plus albumin and subsequently has been negative. Admission and subsequent blood studies have shown a white blood cell count always in the normal range; red blood cell

count of 6 to 7 million, and a hemoglobin of 20.0 Gm.; hematocrit values have been 57 per cent. A sedimentation rate was at the upper limit of normal. His course has been satisfactory. His rate has slowed from the 2:1 block through a shifting 3:1 and 4:1 to now a fixed 4:1 block. He is much more comfortable.

DR. WHITE: He is a big man, always heavy and robust, with a big neck, but he was much more robust looking and evidently edematous when he came in and that is no longer evident. As stated, the abnormalities were chiefly in the abdomen and liver, with evident fluid and edema in the abdominal and chest walls, neck and face and some in the legs, but not much.

I think we might have him in now. Our first impressions were gained before we had some of these studies, the blood study in particular. And when I talked with him yesterday he said he had no complaints. His pulse rate yesterday was regular at about 75 with a 4:1 block and auricular flutter. We have not changed the flutter, but we have obtained a satisfactory heart rate. We have not given him quinidine. He still shows a large abdomen which he has always had he says, but which is much less prominent than when he came in; it is now soft and the liver is not felt, or if it is, it is just at the costal margin. His legs now show no edema and in the face only the cheeks are large; there is no edema left in the upper part of the body. His heart sounds continue to be rather soft and you might expect them to be somewhat distant because of his thick chest wall due to his build, but they seem to be more distant than they should be. There are no murmurs and there is no unusual accentuation of the sounds. At first the veins could be seen in the neck even though there was some edema. Now, although his venous pressure has not returned to normal, it is difficult to see the veins. I have noticed that in other individuals with large necks.

DR. JACOB LERMAN: What is that prominence in the lower jaw?

DR. WHITE: An old wen. It has now been revealed since the edema has disappeared. Dr. Schultz, do you want to comment?

DR. MILFORD D. SCHULTZ: I would just as soon defer to you. Really all you see in the x-ray is a large cardiac shadow with this configuration (Fig. 3, 4, 5). I don't believe it is characteristic of any particular thing. He has no fluid in the chest.

DR. WHITE: Is there a difference in size or do you think they are about the same? There is an interval of only a few days here but our fluoroscopic examination made yesterday showed about the same shadow that this would indicate.



FIG. 3. December 28, 1946. Heart is enlarged without characteristic configuration. FIG. 4. December 31, 1946. Essentially no change over December 28. FIG. 5. January 13, 1947. Despite interval of clinical improvement very little change in the heart shadow; it is possibly a little smaller than previously.

DR. SCHULTZ: It certainly has not changed a great deal.

DR. WHITE: This first film was taken, I think, at the height of his edema, soon after he entered.

DR. SCHULTZ: Yes. The pulmonary vessels are a little more prominent, I think, than they were here. Maybe not.

DR. WHITE: That was at the time his heart rate was 140. The differential diagnosis is, of course, of extreme interest. He was sent in to us because of a suspicion of cirrhosis of the liver; his abdomen was very prominent then. Shortly the diagnosis was changed to congestive heart failure. Congestion was certainly present but whether it was due to myocardial failure remained open to question. The response of his flutter to digitalization has been unusually satisfactory and raises the question of whether this may not, after all, have been in large part congestive failure due to some underlying unrecognized condition in addition to the flutter. We do not see congestive failure resulting from arrhythmia of the nature of flutter or fibrillation alone except in the rarest cases. I have seen a few cases in whom over a period of years heart failure may result from an uncontrolled tachycardia and that remains a possibility in his case, but his severe symptoms developed only about a week before he came in here although he had had some difficulty before that for some months. We don't know when his arrhythmia started.

We naturally thought of pericardial constriction because of the absence of evidence of cardiac involvement except for the flutter and the slight cardiac enlargement, and because of the small arterial pulse pressure. The other day his pulse pressure, when he had lost his edema and his heart rate was good, was still only 25 at 125 mm. systolic and 100 diastolic. On another occasion the blood pressure measured 115 systolic and 90 diastolic. He has had a diastolic pressure

as high as 105 and 110 but always with a small pulse pressure and he showed an increased venous pressure at the same time. At the very beginning, before we had the knowledge of his polycythemia, which though present is not of an extreme degree, we thought that he might prove to be a classical case of constrictive pericarditis, subacute or chronic; but he has improved so rapidly and his congestion now has cleared so completely that that diagnosis must be questioned a good deal. We did a peritoneoscopy at the time he was clearing; that is, he already had lost most or all of the fullness of his abdomen. Dr. Benedict could find nothing wrong and said that the liver looked all right; it did not even seem to him to be enlarged. A few days before the peritoneoscopy he had already had an intensive diuresis and his heart rate had come down. By that procedure (peritoneoscopy), which I think is very helpful in patients suspected of either cirrhosis or constrictive pericarditis and because of their occasional simultaneous occurrence, we have ruled out both peritonitis and obvious liver involvement. Nor was there even any fluid seen in the abdomen at the time of the peritoneoscopy. It had cleared completely.

There is one other interesting point. It is that his electrocardiogram which in addition to showing auricular flutter reveals a right-axis deviation. That is, of course, against any chronic hypertensive heart condition, for such would not be accompanied by a right-axis deviation. This finding has raised the possibility of a cor pulmonale. But there is nothing in the lungs by x-ray examination to indicate a cause for either acute or chronic cor pulmonale. The only possible explanation for a cor pulmonale in his case would be an endarteritis obliterans of the pulmonary vessels. That we have seen in rare cases, but it would be very unusual for such a condition to be accompanied by arrhythmia. One doesn't find arrhythmia

with a cor pulmonale. We do, however, see arrhythmias in pericarditis. It is quite common to find auricular fibrillation or flutter with subacute or chronic constrictive pericarditis, which thus still remains a possibility underlying this man's condition. We have noted such arrhythmias in about one-third of our cases, if I recall correctly. In patients with constrictive pericarditis, auricular fibrillation or flutter or any other tachycardia can precipitate or aggravate symptoms and signs. For a few weeks or months in such cases, after one has controlled the heart rate, one may still find an increase in venous pressure above normal. There are some such patients with a slight degree of tachycardia who can stay well for years if their heart rate remains at a reasonably low level.

The most difficult differential diagnosis is between constrictive pericarditis and myocarditis of unknown cause. We have had two cases of the latter condition operated upon in our series here at this hospital. Both of these patients we thought probably did not have constrictive pericarditis, but because we could make no other diagnosis we considered it our duty to operate upon them. They failed to show pericarditis. One of these two patients we know from a study post mortem had extensive myocarditis of unknown cause with no valvular disease or evidence of coronary heart disease. This same diagnosis remains a possibility in our patient today. The tachycardia due to auricular flutter evidently precipitated the congestion, no matter what the background was. Our patient still has a small arterial pulse pressure; the somewhat high diastolic level at times suggests that he may have been slightly hypertensive. He still has a somewhat high venous pressure but his edema has entirely subsided. His electrocardiogram remains abnormal with flat T-waves that would be consistent with either myocardial or pericardial disease. And he has the polycythemia also. We have wondered whether or not the combination of polycythemia and auricular flutter could have precipitated congestion. I would rather doubt it, at least of this degree. We shall be very glad to have suggestions or a discussion about this unusual case.

DR. JAMES H. MEANS: I would like to ask a question. If the heart enlarges fairly rapidly from intrinsic disease, the pericardium stretches all right and accommodates it, does it not, and you don't get any constriction ordinarily? Well, do you suppose in the early stages of constrictive pericarditis you may have a situation in which you have a pericardium that just isn't as elastic as the normal one is, and then if you had some dilatation you would get constriction when you didn't have it before? In other words, you get constriction when the heart gets bigger, although you

don't when the heart isn't so big. It is a relative matter.

DR. WHITE: That would apply if the left ventricle is primarily constricted. We have not seen such a case in which the right ventricle is involved, which is the commonest type. There the blood is not coming into the heart in the first place. There is a rigid pericardium. Two layers are adherent and bound down on the heart. We have not noted any instances in which the pericardium is thick but not actually constricted, in the ordinary sense. It is true that the tachycardia in our cases has been very important. The constriction of the left ventricle which we have seen in probably two out of three of our cases, has produced some enlargement of the right ventricle and enlargement of the heart that is evident here may conceivably be practically all right ventricle. But the type of failure was due to the right ventricle. There is no evidence of valvular disease or intrinsic pulmonary disease. We will have a better understanding probably in the course of the next few weeks but we may not. But we will try to give you a better report about him. We think it is a picture of a moderate or lesser degree of constrictive pericarditis with a precipitation of failure by the tachycardia, but he may also have some other etiologic factor which is difficult to discover.

DR. BERNARD M. JACOBSON: Would arterial blood oxygen studies help you?

DR. WHITE: Yes, I think so. Also, it would be of some interest to do cardiocatheterization which might reveal increased right ventricular pressure, and it would help to see whether that is an important factor in a question of this sort, where there may be constriction or primary disease in the left side.

A PHYSICIAN: Was he cyanotic?

DR. WHITE: He was not cyanotic.

#### *Editor's Note*

This patient was discharged on the 16th of January 1947. He was seen on the 29th of January in the Cardiac Outpatient Clinic where he was examined by Dr. Edward F. Bland. Physical and electrocardiograph examinations at this time revealed him to be essentially normal with no evidence of cardiac embarrassment. He had normal rhythm. He had led a restricted regime since his discharge and had noted no symptoms of cardiac difficulty. No further diagnosis was reached at this time. Subsequently, Dr. Lewis Dexter of the Peter Bent Hospital performed a venous catheterization on this patient in an attempt to delineate the problem more clearly but without aiding in making a positive diagnosis. At

the present time precise diagnosis of this patient remains somewhat undifferentiated.

## CASE 12

### RECURRENT GRAVES' DISEASE

DR. WALTER BAUER: The patient we wish to present is a man of 60. He came in with a provisional diagnosis of recurrent thyrotoxicosis. You will note that the patient's symptomatology is very similar to that experienced six years ago and is consistent with a diagnosis of recurrent thyrotoxicosis. On physical examination the findings are minimal, and when we resort to the laboratory for confirmation of this diagnosis, particularly as it relates to the basal metabolic rate, we find figures of minus 15 and minus 23. Ten days prior to admission and 14 days before the first B.M.R. he was started on sodium iodide. He was reported to have a B.M.R. of plus 20, done by his local physician. I thought it would be very interesting to present this patient in order to have Dr. Means discuss the question of recurrent thyrotoxicosis; whether it is more frequent in one sex than in the other, and whether it is encountered more often in a particular age group. The first question we put to him in this instance is: Does the man have recurrent thyrotoxicosis? Or do we have to postpone the establishment of that diagnosis for a period of some weeks during which he will be without medication? We also would like to have Dr. Means discuss the treatment of recurrent thyrotoxicosis, as to whether it is treated any differently in an individual 60 years of age as opposed to one in a much younger age group. And if time permits, I for one, would like to have him discuss the present treatment of thyrotoxicosis. Dr. Mellinger.

DR. GEORGE W. MELLINGER: This is a case of Mr. D., No. 560470, who is 60 years old. He was admitted here on January 10, 1947. He is a Russian-Jewish carpenter and his story begins seven years ago. At that time he began to notice increased fatigue on exertion and a feeling of weakness. At the same time, he began to lose weight without change in appetite. During the next three months' period he lost about 17 pounds, going from 202 to 185 pounds, at which time he went to his local doctor for advice. His doctor treated him symptomatically, using no iodides, for the next three or four months. Throughout this entire period the patient had no other symptoms of thyrotoxicosis. Specifically, he had no nervousness, no sleeplessness, no irritability, no tremor, no heat intolerance. His eyes had not been prominent; he had not noticed a mass in the neck; there had been no difficulty in swallowing or speaking. He noticed

no substernal pressure or pain, no palpitation and no change in bowel habit. About five months later he had a B.M.R. which was found to be plus 40 and he was referred to a clinic. There the elevated B.M.R. was confirmed and the diagnosis of masked hyperthyroidism was made. He was placed on iodide therapy and ten days later he developed a pruritic rash on his back, which then disappeared in spite of the continuance of iodides. A subtotal thyroidectomy was done, after which the patient noticed complete symptomatic relief. He had no more fatigability or weakness and his weight began to increase. During the next six months it increased from his preoperative weight of 135 pounds to around 185 pounds. During the next five or five and one-half years his weight remained essentially the same, between 180 and 185 pounds, and he had no more fatigability or weakness.

Then about six months ago, he again began to lose weight. In addition he also noticed increased fatigability and weakness. For these reasons he sought the advice of his doctor again three months ago. His doctor placed him on brewer's yeast tablets, in spite of which he continued to have symptoms. About two weeks ago he went to his doctor again and he was started on potassium iodide, 0.3 Gm. three times a day. The B.M.R. ten days later was found to be plus 20. He also had an upper respiratory infection and his lymphocyte count was about 50 per cent. The doctor thought at that time that the lymphocytosis was probably on the basis of his upper respiratory infection.

We could elicit no history of emotional or physical precipitating factors for this recurrence of thyrotoxicosis, if it is a recurrence. In addition, three or four months ago, the patient began to notice a very mild exertional dyspnea on climbing three or four flights of stairs. There were no other symptoms of cardiac decompensation. There had been no orthopnea, paroxysmal nocturnal dyspnea, ankle edema, ascites, or palpitation.

The social history reveals that the patient was born in Russia near Kiev which is near the ocean. He came to this country in 1907, living for six months near Portland, Oregon, and then moved to Chelsea, Massachusetts.

Physical examination revealed a temperature 99.8°; pulse 80; respirations 24; and a blood pressure of 150/86. A slight lid lag was present. The other ophthalmic signs of thyrotoxicosis were absent. The thyroid gland was enlarged about two times the normal size; the left lobe was somewhat larger than the right; no nodules were present. The gland was moderately firm and nontender. There was no bruit present in the thyroid. An old thyroidectomy scar

was present. The heart was slightly enlarged, the left border of cardiac dullness being 10 cm. to the left of the midsternal line; occasional extra systoles were present. The liver edge was palpable two fingers' breadth below the right costal margin. A capillary pulse was present in the finger nails. The palms were warm and sweaty.

The urinalysis done on admission showed three plus albuminuria but otherwise was negative. Subsequent urines have been negative for albumin. The white blood count was 9,400, with 48 per cent polymorphonuclears, 47 per cent lymphocytes, 3 per cent mononuclears, 1 eosinophile, 1 basophile. Red blood cell count was 5.5 million, hemoglobin 15 Gm. Serum cholesterol was found to be 320 mg. per cent; cholesterol esters 210 mg. per cent; nonprotein nitrogen 24 mg. per cent; bromsulfalein retention 4 per cent. B.M.R. tests one and three days ago were minus 22 and minus 15. A chest plate showed no evidence of substernal extension of the thyroid.

DR. BAUER: As Dr. Mellinger says, the signs of thyrotoxicosis are minimal. There is suggestive lid lag with the only palpable thyroid tissue being in the inferior lobes, more on the left than on the right.

DR. JAMES H. MEANS: If he has any tremor, it is very small. I am not sure that he has any. His hands are warm and moist. His skin in general is moist. I think you can see a little thyroid tissue there as he swallows, and a little bit can be felt, but it is rather minimal. He is a bit flushed, not his face, but the rest of his skin that is visible. Now about eye signs. I would say that he had very minimal or zero eye signs. When did he stop taking the iodine?

DR. MELLINGER: There is some variation in the story. He says just before coming to the hospital, but according to his doctor he stopped two weeks ago.

DR. MEANS: B.M.R. tests were done when?

DR. MELLINGER: One and three days ago.

DR. MEANS: They could be looked upon as being low because of iodine, couldn't they?

DR. MELLINGER: Yes.

DR. MEANS: Was any story obtained that it made him feel any different?

DR. MELLINGER: No, he said it did not change his symptoms at all.

DR. MEANS: Do you know whether during this period of recent weight loss and also during the original period of weight loss he had a poor appetite or big appetite?

DR. MELLINGER: He said the appetite was the same and his caloric intake was approximately the same.

DR. MEANS: It is a somewhat tough job to diagnose whether or not this man has recurrent Graves' disease. I suppose it would be proper to go back to the orig-

inal diagnosis: Did he have thyrotoxicosis seven years ago? I have no doubt that he did. I don't think the clinic would have done a subtotal thyroidectomy on him if they had not been reasonably sure of thyrotoxicosis, and moreover the story given was perfectly consistent with moderately severe thyrotoxicosis at that time, so I would be perfectly willing to accept that. Now, the question is: Has he got it now? That is not so easy to answer. He apparently has some malady now because he is losing weight and feels sick. At least, he feels weak. The data that we have are in some respects equivocal. How can you make a diagnosis of thyrotoxicosis with a cholesterol like that of myxedema and the minus metabolic rate? The metabolic rate might be on the basis of the iodine he has had. We did have a story of the fairly recent plus 20 rate following which he was put on iodine and then he has these minus rates. If that is correct, we might interpret that as a good bit of evidence favoring the diagnosis of recurrent thyrotoxicosis, because one of the things that happens in either the original attack or in recurrences of the thyrotoxicosis of Graves' disease is that the metabolism fluctuates up and down in response to iodine. Usually there is a feeling of subjective improvement with the drop in metabolic rate, but it does not always occur. He apparently has had no subjective impression of having improved during his recent course of iodine, but he only had it for two weeks. But that ought to be enough to make him feel better. The late Henry Plummer told me, and I am sure we observe the same thing, that on iodine a person may feel better in a matter of hours when they are severely thyrotoxic, long before they show any metabolic response. So the picture is not complete. I just cannot take care of that high cholesterol. That is not as easy to dismiss as these low metabolic rates. I don't know what it signifies.

I would like to take the position that thyrotoxicosis is not really a diagnosis, any more than fever is a diagnosis. Thyrotoxicosis means an overactive thyroid, or better it means an oversupply of thyroid hormone to the body and usually that is due to an overactive thyroid.

Now we go through various phases of thought on these subjects. Dr. Albright always prefaces his remarks by saying, "As of today, we think," so and so. We do the same thing and go through different periods as Picasso went through his "blue" period. At the moment I should like to use the word *Graves' disease* to identify what I believe to be an etiologic entity. I think people with no thyrotoxicosis but only eye signs, on the one hand, and people with a big goiter, marked hyperthyroidism and no eye signs



on the other hand, as well as every kind of a combination in between these extremes, in all probability have the same disease. And so I use the term Graves' disease to cover the lot, for want of a better.

So the question becomes: Has this man recurrent Graves' disease? You can have Graves' disease without thyrotoxicosis, so you can have it with minus metabolic rates. Usually we see that in combination with rather marked eye changes, which this man does not have, but, still, I think that the set-up here is not inconsistent with the diagnosis of recurrent Graves' disease, and I suspect that he has it. I am troubled about the cholesterol. So I would put it this way: I cannot, on the basis of seeing this man this morning, be perfectly certain he has recurrent Graves' disease, but I suspect in all probability he has.

Now you asked me quite a string of questions about the general subject that you would like me to answer. First of all, what about the frequency of recurrent Graves' disease? We do not have too good figures on that, but for the whole country about 4 to 5 per cent of cases receiving subtotal thyroidectomies recur. I don't know of any very great difference between sexes. I would suspect it might be more frequent in females but I am not sure. But there is something I am very sure of and that is that it is more frequent in younger people than in older ones. I can remember several cases of young children and young people who have had to have a whole series, as many as three thyroidectomies, before they were relieved of the thyrotoxicosis of Graves' disease.

Now then, how to treat the recurrences? Well, I cannot lay down any general rules about that. I would think that I might lump it with the treatment of the whole disease. I do not think the indications in recurrences are especially different from those in the original attack, except that one might on the whole be a little more conservative in the treatment of the recurrences. And that again involves the question: What is meant by conservative? I will have something to say about that in a moment. What is the conservative treatment? Well, what is the whole situation regarding the treatment of Graves' disease? It was all very simple and lovely until a few years ago. We thought we had a fairly satisfactory treatment. We prepared patients with iodine and did subtotal thyroidectomy and we thought they did pretty well. I must confess that the other day, Dr. Edward Hamlin, one of the surgeons who has joined our thyroid group, who has been doing something of great value, namely, looking up all our cases of Graves' disease for a period of years, said that as he did this he was a bit appalled at the number of postoperative complications. We thought on the medical side, that

the surgeons did very well. They cut a few vocal cords and once in a while got tetany, but on the whole did a pretty creditable job; the preparation with iodine was fairly satisfactory and there were not very many postoperative storms. So that was our more or less standard therapy and we treated the recurrence in the same way if it was bad enough.

Then all these new things arrived. First, radio-iodine turned up. Our colleague, Dr. Hertz, thought of using that for therapy and it was studied extensively, and unquestionably is an effective method of treating Graves' disease in that it relieves the thyrotoxicosis. I try to distinguish between thyrotoxicosis and Graves' disease, and the therapies that I am talking about are symptomatic in that they are aimed at the thyrotoxicosis, and in some cases of Graves' disease there is little or no thyrotoxicosis. Then you don't aim at the thyrotoxicosis. You may have to plan your therapy entirely around the eye situation or something of that kind. But in the classical case, where you are aiming at thyrotoxicosis, you have a choice now between thyroidectomy or putting a quietus on the overactive thyroid by means of radio-iodine. We used to use x-ray to do the same thing. Then along came a flock of drugs called antithyroid or goitrogenic drugs; you know that they have their vigorous proponents who think surgery is outmoded and obsolescent. I will merely tell you, to answer Dr. Bauer's question, where this particular group in the Massachusetts General Hospital stands at the present day with regard to the treatment of Graves' disease with thyrotoxicosis. We have a choice, really, of three methods. I will say one thing about the antithyroid drugs of which I am sure, which is that the advent of these drugs has made it possible for us to prepare the patient for operation very much better than we had been able to do previously. One can give the patient to the surgeon in a completely euthyroid state and also with an involuted thyroid gland, so he has a better chance to do a good job and have less postoperative disturbance than he ever had before. I think that is certain. As between that program, radio-iodine, and prolonged treatment with antithyroid drugs, you will find the greatest possible difference of opinion. There are the proponents of radio-iodine and the proponents of antithyroid drugs alone. Here, we still believe that perhaps the best way from the patient's point of view is to operate on them, most of them, after doing the kind of preparation I have described. We depart from this program under certain circumstances. We depart from it in certain cases because we want to get a series of radio-iodine treated cases in order to evaluate that method of treatment. But that is not, you might say, our



standard therapy. We do not treat any patients with prolonged antithyroid drug. That does not altogether mean that we disapprove of it completely. We realize that other people are using the antithyroid-drug-alone program and they will pile up lots of data and ultimately the best treatment will emerge. In general, whenever a new therapy is proposed and tried, there are always a lot of enthusiasts, genuinely enthusiastic about it, sometimes overenthusiastic. What happens is that the therapy either survives or else it doesn't, as it is tried out by the profession.

And so it is a choice between several therapies, any of which will, in a large number of cases, cure the patient. I probably have confused you completely about the therapy of Graves' disease, but I don't know how I can do any better, because the situation is confusing. I have told you what we think here.

Now, about this particular patient, what will you do about him? I don't think I quite want to stick my neck out as to just what I would do for him yet. If he has a recurrence it is very mild. Some very mild recurrences are handled by the old-fashioned method of nothing but the prolonged use of iodine. And one can use irradiation. I would rather see him a little longer and get the problem added up a little better before I commit myself as to just how to treat this particular patient. I would want to see what his metabolic rate does when he has a month off iodine instead of two weeks. It may bounce up again. That would give us a more accurate evaluation. I would like to get a little more data. I would like very much to know what the protein-bound iodine of his blood is, because we have found that of very great value in borderline cases where we are confused about the diagnosis and some of the data are equivocal. Another trick we have used is to give radio-iodine in a diagnostic way and see how much the thyroid will take up. If it is hyperplastic and overactive it will take more of a given dose than will the normal gland. That would be useful here. And, of course, there are other things, the creatine tolerance test of Shorr, for example. I would like to see what the patient looks like when he has been a month off iodine and then re-evaluate the situation. In the old days, when we got in a jam of this kind and could not make up our minds whether the patient had Graves' disease or not, or didn't know what to do about it, we pursued a policy of watchful waiting, which is perfectly reasonable. Stop all medication and see what the picture is when it is fully developed, and then you can make your plans to deal with it. If this fellow has a fairly severe thyrotoxicosis now, one might reach the position of wanting to take out some more thyroid or want to treat him by one of these other methods.

DR. BAUER: We plan to discharge him from the service in a day or so and have him report in about a month's time for re-evaluation of his clinical picture.

DR. MEANS: I wish you would ask my colleagues whether they agree with what I said. I would like to hear from Dr. Lerman about the cholesterol.

DR. JACOB LERMAN: I should say that this cholesterol value would be consistent with the drop in metabolism. The chances are he did not have a B.M.R. of plus 20, he probably had an infection at that time, and probably had a true B.M.R. of plus 5 or plus 10, and a drop of metabolism is not inconsistent with the taking of iodine, so he may have had a cholesterol of 320 at that time and the drop in metabolism would raise it to that level.

DR. BAUER: The patient himself would prefer not to have surgery. I raise the question that if we could prove the diagnosis of recurrent Graves' disease with thyrotoxicosis as to whether he could be a good candidate for radio-active iodine.

DR. MEANS: There is one thing to be said for radio-active iodine. We are using the 12-hour isotope that we got from the cyclotron at Massachusetts Institute of Technology and there is no question but that it cured some patients and really was very impressive, but now we cannot get it any more. The only iodine we can get now is the 8-day isotope, which we get from the Manhattan project at Oak Ridge, Tennessee. That is all they can give us, and we don't know what the right dose is. Dr. Earle Chapman is working on that. Naturally, he started on a low dosage and is working up, and he showed me his notes this morning which we both agreed were not impressive. We thought probably that the dosage used was inadequate. But we haven't at the moment a very good radio-iodine program to offer this patient.

#### *Editor's Note*

February 12, 1947. This patient was discharged from the hospital on the 17th of January 1947 with a tentative diagnosis of recurrent Graves' disease. He was taken off all iodine on the 10th of January and had received no other therapy except a mixed vitamin capsule from this time until seen on the 12th of February. On re-examination at that time, it was found that his subjective complaints were precisely the same as they had been. Physical examination was normal except that the thyroid was about one to one and one-half times its normal size. On questioning the patient denied that he had felt better during the period of iodine therapy. It was the opinion of the thyroid clinic that the patient did not have recurrent thyrotoxicosis and that the symptoms would have to be explained on some other basis.

# CASE REPORT

## Diffuse Carcinomatosis of Lungs and Subacute Cor Pulmonale \*

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*This case report illustrates changes in the right heart which may occur in pulmonary disease of relatively short duration.*

This 58-year-old white male had been well until approximately six weeks before admission to the hospital. At that time he began to complain of mild epigastric distress and anorexia. He had lost five to ten pounds during the previous several weeks and had had an occasional grossly bloody stool. A chest film showed a fine, diffuse nodularity, present in all lobes, which was suggestive of either silicosis or miliary tuberculosis, except for the fact that the distribution was not as uniform as is usually seen in these diseases. The cardiac silhouette was within normal limits. The patient was advised to enter the hospital for study with a tentative diagnosis of carcinoma of the stomach. Approximately eight days before admission, the patient developed dyspnea, orthopnea, and substernal pain, and was obliged to cease work. During the subsequent week, these symptoms became progressively worse, and he was admitted to the hospital two days before his originally scheduled appointment.

His past history was noncontributory.

Physical examination revealed a well developed, well nourished man, slightly cyanotic, dyspneic, and complaining of substernal pain. His temperature was 38° C., pulse 120, respiration 32, and blood pressure 90/70. The skin was cold and moist. Breath sounds were vesicular, percussion normal, and no râles were heard. Systolic and diastolic murmurs were heard over the entire precordium, but were best heard at the left sternal border in the third and fourth interspaces. There was moderate epigastric tenderness and the liver was palpated 4 cm. below the costal margin. No other organs or masses were palpable. The extremities showed no edema.

An electrocardiogram taken on admission showed sinus tachycardia. The T-waves were inverted and the S-T segments elevated in lead III and in chest leads V<sub>1</sub> and V<sub>3</sub>, suggesting posterior myocardial infarction.

The patient was placed in an oxygen tent. His respiratory rate became increasingly rapid and cyanosis deepened. He died three hours after admission, before further studies could be carried out.

### AUTOPSY (9328)

The heart weighed 450 Gm. The pericardium was not remarkable. There was a slight fat infiltration of the myocardium of the right ventricle, but otherwise the myocardium was normal. The left ventricle measured 14 mm. in thickness, the right ventricle 6 mm. The latter was dilated to approximately twice its expected volume and its enlarged columnae carnae were markedly flattened. The right atrium was moderately dilated. The left ventricle and atrium were normal in size. The tricuspid valve measured 13.5 cm. in circumference at the ring; the pulmonic valve 8.5 cm., the mitral 10.8 cm., and the aortic 8.0 cm. The mitral leaflets showed slight nodular thickening along the line of closure. The remaining valve leaflets were delicate and normally formed. The coronary arteries showed slight arteriosclerosis, but without significant stenosis or occlusions. The aorta showed moderate arteriosclerosis. The pulmonary artery measured 6.8 cm. in circumference at its origin. Its trunk, primary and secondary branches were not remarkable.

The pleural cavities were obliterated by fibrous adhesions.

The right and left lungs weighed 710 and 670 Gm. respectively. Crepitation was slightly and uniformly decreased. Cross-sections were similar in all lobes, dark red, freely bleeding, and slightly bulging. An extremely fine, diffuse nodularity could be palpated, but the individual nodules were too small to be seen grossly.

\* From the clinicopathologic conferences of the Institute of Pathology, Western Reserve University and University Hospitals of Cleveland, Ohio.

The wall of the fundic portion of the stomach was diffusely indurated in its entire circumference. The mucosa of the greater curvature was thrown into thick rugal folds measuring up to 3.0 cm. in thickness, and the wall of the stomach measured 2.5 cm. in thickness in this region. The mucosa of the lesser curvature showed a relatively flat rugal pattern. The mucosa throughout was bright red, showed prominent mosaic markings, but was not ulcerated. Cross-sections of the indurated wall showed pale gray, poorly defined submucosal and muscular layers.

Adjacent to both lesser and greater curvatures were several firm lymph nodes measuring up to 1.5 cm. in diameter. The cross-sections were pale gray, bulging, and homogeneous. Several nodes were found in the posterior mediastinum measuring up to 2 cm. in diameter, which were similar except for associated moderate anthracosis.

The significant final anatomic diagnoses are listed below.

**Microscopic Description.** Sections of the lungs showed small nests of tumor cells scattered throughout the peritruncal lymphatics of all lobes. These cells were of varied appearance, some being of the signet ring type, while others showed hyperchromatic nuclei, varied in size and shape, and in general had the usual characteristics of the undifferentiated epithelial cell. With perhaps one exception, the carcinoma did not invade the arterial walls. Almost all of the small arteries and arterioles were the seat of pathologic change, and in well over 50 per cent, these changes were of marked degree. Fibroblastic proliferation of the subintimal connective tissue was prominent causing marked stenosis, and in some instances, obliteration of the lumina. Whether or not the seat of intimal proliferation, many of the small arteries and arterioles contained masses of fibrin, hyaline material, and blood cells. Many of these thrombi showed organization and canalization. Occasionally small clumps of tumor cells were demonstrated within the lumina. The vessel walls were moderately infiltrated by lymphocytes, plasma cells, and occasional polymorphonuclear neutrophils. Moderate acute passive hyperemia and slight pulmonary edema were also present.

Sections of the stomach showed foci and strands of undifferentiated epithelial cells, extending throughout the submucosal and muscular layers, with an associated great increase in connective tissue. The cells varied in size, shape and staining reaction, showing hyperchromatic nuclei, and frequent atypical mitotic figures. Lymphatic invasion was readily demonstrable. The mucosa and submucosa were also diffusely

infiltrated with lymphocytes, plasma cells, and polymorphonuclear neutrophils and eosinophils.

Sections of regional and mediastinal lymph nodes showed metastases which obliterated the normal pattern.

*The significant final anatomic diagnoses* were hypertrophy and dilatation of the heart especially manifest in the right ventricle; diffuse carcinomatosis of the lungs, secondary to cirrhus carcinoma simplex of the stomach; subacute and chronic pulmonary thromboarteritis and arteriolitis; metastatic carcinoma of regional and mediastinal lymph nodes; acute and chronic passive hyperemia of the liver; acute passive hyperemia of the spleen.

## COMMENT

This patient died of cardiac failure incident to cor pulmonale. The cor pulmonale was attributed to the marked degree of pathologic change in the small arteries and arterioles of the lungs. These changes took the form of a subacute and chronic thromboarteritis and arteriolitis, which is believed to be secondary to the diffuse carcinomatosis, with its primary a scirrhus carcinoma simplex of the stomach.

Diffuse infiltration of the pulmonary peritruncal lymphatics is not infrequent, and has been described in association with primary carcinoma of stomach, bronchus, breast, rectum, kidney, ovary, tongue, prostate, and liver. The most common primary tumor producing this type of metastases has been the scirrhus carcinoma of the stomach. In 1889, Girode<sup>1</sup> first described the occurrence of endarteritis of the pulmonary arteries in the presence of pulmonary lymphangitic carcinomatosis. Schmidt<sup>2</sup> in 1897 reported tumor cells from carcinoma of the stomach in branches of the pulmonary artery, and he pointed out that narrowing and obliteration of the pulmonary arterioles were responsible for right ventricular hypertrophy in this case.

Since this time several cases have been described, of pulmonary carcinomatosis with associated obliterative endarteritis, which together have acted to produce cor pulmonale, right ventricular hypertrophy, and finally failure and death. Relatively recent articles with more or less complete bibliographies on pulmonary carcinomatosis with secondary obliterative endarteritis, are those of Greenspan,<sup>3</sup> Wu,<sup>4</sup> Mason,<sup>5</sup> Jarcho,<sup>6</sup> and Schattenberg.<sup>7</sup> In some cases, nests of tumor cells have been prominent within the lumina of the small arteries and arterioles, while in others, the tumor cells are much more numerous in the perivascular lymphatics. As yet, it has not been proved which, or actually

if either, is responsible for the concomitant endarteritis. The carcinomatous emboli are most commonly believed to be caused by involvement of the thoracic duct, with subsequent dissemination into the venous system. The lymphatic spread is usually believed to be by way of the regional lymph nodes, thence to the tracheal and mediastinal nodes. Involvement of the latter presumably produces lymph blockage, with consequent centrifugal dissemination throughout the lungs.

The disease has been fairly well established as a clinicopathologic entity, and is characterized by a rapid development (days or weeks) of symptoms of right ventricular strain, in a patient without previous history of cardiorespiratory disease. A primary carcinoma is present, usually in the stomach, the symptoms of which are often mild, or else masked by respiratory symptoms. The latter consist of dyspnea, tachypnea, unproductive cough, and cyanosis. Physical examination often reveals nothing significant. The course is rapidly fatal after the first appearance of respiratory disturbances. Autopsy reveals one or all of the following: Diffuse infiltration of the pulmonary perivascular and peribronchial lymphatics; carcinomatous emboli; and obliterating endarteritis with recent and organizing thromboses of the small arteries and arterioles. There is always associated right ventricular hypertrophy and dilatation, and a primary carcinoma, usually of the stomach.

Clinically, the reported cases can be divided into two groups (1) those cases in which the patient has developed rapidly, symptoms of right ventricular strain without evidence of associated malignancy and (2) those cases with similar symptoms but in which there is evidence of associated malignant disease. In 1937, Brill and Robertson<sup>8</sup> reported a case, and col-

lected two from the literature which fit into the former group. They suggested the term "subacute cor pulmonale" as an aid in diagnosis for this group of cases, as compared with the terms acute cor pulmonale, usually referring to pulmonary emboli, or chronic cor pulmonale, caused by such diseases as the pneumoconioses. In 1940, Mason<sup>5</sup> described a case with the carcinoma primary in the breast; in 1942 Brill and Krygier<sup>9</sup> reported another case in which the tumor was believed to be primary in the stomach. Both of these cases fit into the group called subacute cor pulmonale. Another case is reported here which clinically and pathologically fits into this group.

#### BIBLIOGRAPHY

1. Girod , J.: Lymphangite cancr use pleuropulmonaire sans cancer du poumon, Arch. g n. de m d., 1:50, 1889 (quoted by Greenspan).
2. Schmidt, M. B.: Ueber Krebszellenembolien in der Lungenarterien, Verhandl. d. deutsch. Naturforsch., Braunschweig, 1897, No. 15, p. 11 (quoted by Greenspan).
3. Greenspan, E. B.: Carcinomatous endarteritis of pulmonary vessels resulting in failure of right ventricle, Arch. Int. Med., 54:625-644, 1934.
4. Wu, T. T.: Generalized lymphatic carcinosis of lungs, J. Path. & Bact., 43:61-76, 1936.
5. Mason, D. G.: Subacute cor pulmonale, Arch. Int. Med., 66:1221-1229, 1940.
6. Jarcho, S.: Diffusely infiltrative carcinoma; hitherto undescribed correlation of several varieties of tumor metastasis, Arch. Path., 22:674-696, 1936.
7. Schattenberg, H. J., and J. F. Ryan: Lymphangitic carcinomatosis of lungs, Ann. Int. Med., 14:1710-1721, 1941.
8. Brill, I. C., and T. D. Robertson: Subacute cor pulmonale, Arch. Int. Med., 60:1043-1057, 1937.
9. Brill, I. C., and J. J. Krygier: Subacute cor pulmonale, due to metastatic carcinomatous lymphangitis of the lungs, Northwest Med., 41:319-321, 1942.

## WHAT'S YOUR DIAGNOSIS?

The patient was a 31-year-old obese male professional dancer who was admitted to the Medical Service on July 1, 1942 complaining of weakness and fatigability.

During the eight months prior to admission he had developed gradually progressive weakness, fatigability and exertional dyspnea, which for the last two weeks had been severe and he was confined to bed. For three months there had been increasing anorexia. During the last two weeks he had developed edema which began in his ankles and increased to involve

the entire lower extremities. During this time he also complained of increasing hoarseness, a mild non-productive cough and diarrhea without abdominal cramps. There was no precordial pain, orthopnea, nausea, vomiting, jaundice, clay-colored stools, abdominal pain or chills or fever. He gave a history of vague indigestion and some intolerance to fatty foods which he had noticed for several years. On one occasion he described a small hematemesis. There was no history of bloody or tarry stools. However, he stated that for a year hemorrhoids had bled mod-

erately with almost every bowel movement. For four years he had been accustomed to drinking 1 to 1½ quarts of wine daily. The past history was otherwise not remarkable and he described good general health prior to the onset of his illness. There was no history of rheumatic fever or syphilis.

Physical examination revealed an obese, pale, dyspneic, slightly orthopneic man who appeared acutely and critically ill. He was of pyknic build, with obesity predominately of the trunk, and had a striking "eggshaped" head and tapering fingers. T. 100.2°. P. 120. R. 32. B.P. 120/60. There was considerable pallor of the skin and mucous membranes. There was no jaundice. Massive pitting edema was present over the lower extremities and lower trunk. There was no significant glandular enlargement. The eyes were quite prominent but were otherwise not remarkable except for the presence of a small white scar on the right retina. The voice was hoarse. The pharynx was slightly injected. The tongue was rather smooth but not reddened. The neck veins were distended. The thyroid was not enlarged. The lung fields were not remarkable except for a few scattered coarse rhonchi. The heart was described as enlarged to the left and right with the apex almost at the anterior axillary line. The heart sounds were rapid and

of poor quality and there was a gallop rhythm at the base. The second sound at the pulmonic area was more prominent than at the aortic area. There were no murmurs. The rhythm was regular. The pulse at the wrist was weak and thready. Marked obesity of the abdomen made examination difficult. The liver was enlarged and tender extending down to the level of the umbilicus. The spleen was not palpable. There was no evident ascites. The genitals were small. Rectal examination revealed the presence of external hemorrhoids which bled readily. Neurologic examination was negative.

He was put on a Karrell diet and digitalized. The use of an oxygen tent was necessary. There was very little response to a mercurial diuretic although there was no oliguria. Because of the finding of a severe anemia he was given very cautiously two small (250 cc.) transfusions of whole blood. He received no other significant medication except for parenteral thiamine chloride. During his brief course in the hospital he ran a low-grade fever (100–101°). There was a tachycardia ranging from 110 to 130. He showed no improvement. On the fourth hospital day his dyspnea increased, he developed signs of acute pulmonary edema, his blood pressure dropped and he died.

#### LABORATORY DATA

(Complete as taken from the record)

##### Blood

HOSP. DAY	RBC	HGB.	VOL. PACKED RBC	WBC	NPN	ICTERUS INDEX	CO <sub>2</sub> COMB. POWER
1	900,000	1.5 Gm.	9	7,500			
2	880,000	3.3 Gm.		6,650	48		48.6 vol. %
3	870,000	4.0 Gm.		4,100			
4					68	15	44.0 vol. %

Differential: (1st Hosp. Day) 42% segmented, 49% lymphocytes, 2% monocytes, 7% smudge. "Segments are of the toxic variety—vacuolated. Lymphocytes small with little cytoplasm."

Kahn: Negative.

Cholesterol: (4th Hosp. Day) 131

Venous pressure: (2nd Hosp. Day) 180 mm. saline.

##### Urine

HOSP. DAY	SP. GR.	ALB.	SUGAR	BILE	MICROSCOPIC
1	1.011	1+	0		Numerous oxylate crystals. Rare RBC and WBC. No casts.
2	1.013	0	0		Numerous uric acid crystals. Rare RBC and WBC. No casts.
3	1.011	tr.	0	0	8–10 RBC/HPF. No WBC or casts. Numerous uric acid crystals.

Stool: (2nd Hosp. Day) Bile present. No occult blood.

Portable Chest Plate: (1st Hosp. Day) Unsatisfactory for reading. Apparently there were no gross pulmonary lesions.

Electrocardiogram: (2nd Hosp. Day) Rate 125; P-R. 16; QRS .06; small Q<sub>s</sub>; ST 1 and 2 depressed with diphasic T<sub>1</sub> and T<sub>2</sub>; ST<sub>3</sub> elevated with inverted T<sub>3</sub>.

Answer to WHAT'S YOUR DIAGNOSIS in the January Issue

Subacute Yellow Atrophy (Sixteen per cent of the answers received were correct.)

# Clinicopathologic Conference

ROBERT W. WILKINS, M.D. and KENNETH MALLORY, M.D.

DEPARTMENT OF MEDICINE

DEPARTMENT OF PATHOLOGY

BOSTON UNIVERSITY SCHOOL OF MEDICINE

BOSTON, MASSACHUSETTS

A 48-year-old housewife was admitted to the hospital for the fourth time on July 30, 1945, in coma with generalized convulsions.

**First Admission:** July 4, 1943–July 11, 1943. For the past year the patient had suffered from palpitation and dyspnea on exertion, occasional dizzy spells and frontal headaches. For the past nine months orthopnea had been present, along with intermittent swelling of the ankles and blurring of vision. There was moderate urinary frequency and nocturia. Two weeks before entry a nosebleed required packing. Two days before entry nosebleed recurred and required admission.

**P.H.:** Four uneventful pregnancies. At 32 years of age there was a severe attack of migratory polyarthritides; occasional mild joint pains had been felt since then. In 1937 she had been told her blood pressure was elevated. Nine months before this admission, a physician found it to be "280."

**F.H.:** Mother died of a heart attack at 48 years of age. Father died of a cerebral hemorrhage at 65. One sister has hypertension.

**P.E.:** Temperature 98.6°; pulse 104, respiration 24. The patient was an extremely obese, white female lying comfortably in a semisitting position, mentally clear and co-operative. Optic fundi showed A.V. nicking, a few light areas suggestive of old hemorrhage, and very slight papilledema bilaterally. There was a bloody pack in right nostril; a few petechial hemorrhages on soft palate. There were a few fine inspiratory râles at both lung bases. The heart was percussed to the left anterior axillary line in the fifth intercostal space; the rhythm was regular with many premature beats. A grade II systolic murmur was heard at the aortic valve area; the second aortic sound was considerably accentuated. B.P. 300+/160. Abdominal examination negative. Neurologic examination negative. Weight 234 pounds.

**LAB. DATA:** Urine specimens showed concentration to 1.020, 1 to 4 plus albumen, rare WBC and RBC,

many hyaline and granular casts in initial specimen, but none in subsequent ones. Hgb. was 60–70 per cent, RBC 4.50 million, WBC 10,400. The blood Hinton test was negative. NPN was 27 mg. per 100 cc. Vital capacity was 2.4L; the circulation time (paraldehyde) 4 seconds, with decholin 17 seconds. Venous pressure was 70 mm. water. PSP excretion 15 min.—5 per cent, 2 hours—35 per cent. Urine culture did not reveal any pathogens. A seven foot chest film showed widening of the aorta, enlargement of the heart and cloudiness at the lung bases. The EKG suggested left ventricular enlargement.

**COURSE:** The patient was treated with a low caloric diet, restricted salt intake, ammonium chloride, phenobarbital, and was digitalized in 36 hours. A sedation test with 7½ gr. sodium amytal did not produce any significant fall in blood pressure although by the end of the fifth day in bed it declined to 240/140.

**Second Admission:** August 21, 1943–October 2, 1943. One week before this admission there occurred sudden onset of weakness of the right arm and leg with transient shaking of the right arm. A local physician doubled the digitalis dosage, and because of the resulting nausea the patient was readmitted.

**P.E.:** Temperature 99.4°, pulse 108, respiration 20. There was poorly defined tenderness and pain of all extremities. The optic disks were blurred. Showers of fine râles were heard at the lung bases. The heart examination was as previously except that P<sub>2</sub> was now accentuated and an apical systolic murmur was heard. The B.P. was 280/160. There was slight but definite weakness of the right arm and leg, no facial weakness. The deep tendon reflexes were slightly more active on the right side.

**LAB. DATA:** WBC were 14,000 to 8,000; NPN 25 and 27 mg. per 100 cc. CO<sub>2</sub> combining power was 54 vol. per cent. The gastro-intestinal series was negative. X-ray following dye showed impaired filling of the gall bladder. Lumbar puncture yielded clear fluid with initial pressure of 250; the fluid was negative.

COURSE: Digitalis was omitted for two weeks, ammonium chloride and phenobarbital were continued and ferrous sulfate was also given. There were severe headaches not relieved by magnesium sulfate given intramuscularly. During the first three weeks, there were frequent episodes of nausea and vomiting; the temperature rose occasionally to 100°. During the second week she was disoriented, confused and had hallucinations. Gradually all these symptoms improved and the patient was discharged on a maintenance dosage of 0.1 Gm. (1½ gr.) of digitalis. The weight was 192 pounds.

Third Admission: October 26, 1944–November 6, 1944. The patient had remained moderately well until two weeks before admission when there occurred a period of coma which lasted several hours. Since then there were headaches, dizziness and tinnitus; there were frequent episodes of disorientation and confusion. On the morning of entry she again became unconscious.

P.E.: Temperature 100.8°, pulse 106, respiration 24. The right optic fundus showed patches of exudate, and on the left there was papilledema. The lungs were clear. The reflexes were normal. B.P. 250/160.

LAB. DATA: Hgb. 88 per cent, WBC 6,500. Urines ranged in specific gravity from 1.010 to 1.021, the albumen 0 to 1 plus; there were occasional RBC and WBC. The NPN was 33 and 47 mg. per 100 cc. The CO<sub>2</sub> combining power was 59 vol. per cent. Lumbar puncture yielded clear fluid with an initial pressure of 400 mm. and a final pressure of 205 after 12 cc. were removed. There were no cells and the Pandy test was negative.

COURSE: Venesection was performed and sedative medication continued after the patient regained consciousness soon after entry. The blood pressure gradually declined to 245/135. After several days symptoms had largely cleared, and the patient was discharged.

Final Admission: July 30, 1945–August 3, 1945. Since her last hospitalization, the patient had lived a bed-and-chair existence. There were numerous brief attacks of confusion and disorientation with less frequent convulsive seizures. Two days before admission she became stuporous and gradually sank into coma. On the day of entry convulsions occurred.

P.E.: Temperature 103°, pulse 140, respiration 40. The patient was comatose, with frothy sputum and mucus escaping from the mouth. About every ten minutes she experienced a convulsive seizure, usually starting over the face and spreading to the extremities, mainly involving the left side of the body. The pupils were small and equal, and reacted poorly to

light. Optic fundi were poorly visualized, but extreme narrowing of arterioles, old hemorrhages and blurred disks were seen. The lungs were clear. The heart examination was as previously. B.P. was 280/150. The deep tendon reflexes were generally hyperactive. A positive Oppenheim and a Babinski sign were elicited on the left side.

LAB. DATA: Three lumbar punctures yielded clear fluid with initial pressures ranging from 110 to 160; there were no cells nor increases in protein. Two urines showed a specific gravity of 1.012, albumen 2 to 4 plus, 0–2 WBC and RBC. WBC were 18,000 to 12,000; Hgb. 12 Gm.; hematocrit 31. The NPN on successive hospital days was 54, 76, 123, 119, 187 mg. per 100 cc. The CO<sub>2</sub> combining power was 54, 46, 36, and 39 vol. per cent; chlorides 88, 80 and 75 m.eq./L.

COURSE: The patient was treated with penicillin, oxygen, glucose in saline solution and hypertonic solutions of glucose intravenously, but failed to improve. The seizures became less frequent, but coma persisted and the temperature rose as high as 107° on the third day. The blood pressure remained fairly constant. During the last three days the urine output totalled less than one liter. Finally the pulse became very rapid and thready, respirations irregular, and the patient died.

#### CLINICAL DISCUSSION BY DR. WILKINS

This 48-year-old housewife first learned that she had high blood pressure eight years before her death from it. Three years before, her pressure was said to be "280" and two years before, it was known to be greater than 250/150. From these measurements alone, one could have prognosticated that she was running greater than a 75 per cent risk of being dead within five years, and more than a 50 per cent chance of dying with a cerebral accident. For statistical analysis has shown that an extreme elevation of the blood pressure is one of the most serious prognostic signs in hypertensive cases, especially as regards the danger of cerebral accidents which account for about 40 per cent of the fatalities. To make matters worse, our unfortunate patient also had had for at least three years before death palpitation, dyspnea on exertion, orthopnea, and edema of the ankles—the signs and symptoms of cardiac strain and impending myocardial failure which cause another 40 per cent of all hypertensive deaths. She also complained of dizziness, headache, blurring of vision, urinary frequency and nocturia, and, finally, of a furious nasal hemorrhage which necessitated admission to the hospital.

On physical examination she was found to be ex-

remely obese, with grade III hypertensive retinopathy and marked cardiac enlargement, confirmed by roentgenographic and electrocardiographic examination. Blood pressure was over 300/160. Neurologic examination was negative.

Renal function studies showed albumin, casts, and rare white and red blood cells in the urine; a normal NPN and a reduced PSP excretion. Circulatory measurements were within normal limits. On symptomatic treatment, including digitalization, she improved. The blood pressure fell to 240/140, emphasizing the fact that digitalization does not increase the blood pressure of hypertensive cardinals.

One month later she was re-admitted to the hospital because of a right hemiparesis. On admission she was found to have frank papilledema, signs of pulmonary congestion, and a blood pressure 280/160. Lumbar puncture revealed the pressure of the spinal fluid to be elevated to 250 mm. of water, but the fluid, itself, to be normal.

During this admission the patient complained of severe headaches, not relieved by intramuscular magnesium sulfate, and also of mental confusion, hallucinations, episodes of nausea, vomiting, and low-grade fever. These findings suggested that the patient was suffering from cerebral disturbances of hypertensive origin, or so-called "hypertensive encephalopathy." Part of the picture, at least, seemed to be of a functional or reversible nature since it subsequently cleared.

It is interesting to speculate upon the nature of the cerebral disturbances. The pathology found in the brain at postmortem examination of hypertensive patients of this severe type is of three kinds: (1) hemorrhagic, (2) thrombotic, and (3) edematous, frequently appearing together in varying proportions. When correlated with the clinical course in these patients, the occurrence of miliary hemorrhages or infarcts seems to account for episodes of vertigo, aphasia, hemiparesis, staggering and personality change, whereas cerebral edema characteristically is associated with symptoms of increased intracranial pressure such as headache, nausea, vomiting, drowsiness and mental dullness. A large cerebral hemorrhage or thrombosis, on the other hand, usually causes the classical signs and symptoms of a major cerebral accident. One gets the impression from clinical evidence that simple thrombosis is just as frequent a cause of such major cerebral accidents in hypertensives as actual hemorrhage, since it is not at all uncommon for a hypertensive patient to suffer a sudden hemiplegia without any loss of consciousness or other serious disturbances. The fact that our pa-

tient never developed chemical or cellular abnormalities in the spinal fluid is evidence, admittedly not conclusive, against the presence of a large cerebral hemorrhage or infarct.

During the last year of her life our patient suffered primarily from a repetition of her cerebral symptoms, with many episodes of headache, dizziness, tinnitus, confusion and complete coma. Blood and spinal fluid pressures remained high, except after specific therapy which at times relieved the patient. However, she finally began to have convulsive seizures involving mainly the left side of her body and associated with pyramidal tract signs on the left. Coma and a high fever, probably also cerebral in origin, along with renal failure were the terminal events in the patient's illness.

The remarkable thing about this patient is not that she died of her disease but that she lived so long with it. On the basis of every criterion that we have for hypertension she was an extremely poor risk. The bad family history, the sustained high blood pressure, the grade IV retinopathy, the marked cardiac enlargement and failure, the repeated cerebral episodes and high spinal fluid pressure, all were of a type that even singly in a hypertensive patient point to a short duration of life. While essential hypertension may run a benign course for many years apparently without causing serious organic disturbances, we have learned to fear the development of such grave prognostic signs as these, especially when they seem to be rapidly or even steadily progressing.

The severity of this patient's disease raises the question of whether it should be diagnosed malignant hypertension. Of course, clinically speaking, this is merely a matter of definition, but we should always attempt to correlate our clinical diagnosis as accurately as possible with the pathologic findings. Thus, we have come to associate benign or essential hypertension with benign or hyaline arteriosclerosis, and malignant hypertension with malignant or hyperplastic arteriosclerosis especially in the kidney. If uremia supervenes we may expect to find necrotizing renal arteriolitis. I hope that Dr. Mallory will comment more fully on the pathology of these different states. The clinical diagnosis of malignant hypertension is one that we reserve for a disease, usually of younger people, that progresses rapidly to a fatal termination, and is associated with a marked loss of weight and the most severe signs of acute generalized arteriolar disease especially in the eyegrounds, kidneys and brain. At the most I would say that our patient suffered a terminal malignant, uremic phase, which



was but the *coup de grace* of a chronic essential hypertension.

Could the hypertension possibly have been secondary to primary renal disease? The family history of hypertension, the obesity, the past history of four uneventful pregnancies and the absence of notable renal disturbances until terminally make this diagnosis most unlikely. Therefore my final diagnoses in this patient would be: (1) Chronic, essential arterial hypertension with a terminal, malignant and uremic phase; (2) extensive hypertensive cardiovascular-renal disease with cardiac hypertrophy and myocardial failure; (3) diffuse encephalomalacia with fresh petechial cerebral hemorrhages, and cerebral edema; (4) ? major cerebral vascular accidents, old on the left, fresh on the right.

## PATHOLOGIC DISCUSSION BY DR. MALLORY

### ANATOMIC DIAGNOSES

1. Encephalomalacia  
Right occipital lobe, recent  
Left occipital lobe, old
2. Hypertensive heart disease
3. Benign, with superimposed malignant, nephrosclerosis
4. Chronic passive congestion with central hemorrhagic necrosis of liver
5. Bronchiolitis
6. Chronic cholecystitis with cholelithiasis
7. Leiomyoma of uterus

The brain showed a small, old yellowish area of infarction in the left occipital lobe at posterior extremity of the fusiform gyrus. This was 1.2 cm. in diameter. There was also a fresh area of softening 4 cm. in diameter, in right occipital lobe. The vessels at base of brain were sclerotic but no obstruction could be demonstrated.

The heart was hypertrophied, weighing 640 Gm. The left ventricle measured 2.5 cm. in thickness; the

right 0.5 cm. There was no dilatation. There was slight thickening of edges of mitral valve, probably rheumatic in origin but too slight to cause stenosis or regurgitation. The coronaries were somewhat thickened but lumens did not seem narrowed. Histologically there were small areas of old fibrosis in myocardium.

The kidneys were equal in size and similar in appearance. The combined weight was 370 Gm. The capsule stripped easily revealing a somewhat pale, diffusely granular surface. The cortices were somewhat narrowed. Microscopically there was marked hyaline arteriolar sclerosis, but also slight hyperplastic arteriolar change. There were also scattered fibrosed glomeruli with atrophy of the associated tubules. There was no evidence of renal decompensation.

### COMMENT

Pathologically this seems to be a fairly typical example of essential hypertension in which cerebral manifestations predominated and were chiefly responsible for death, but in which concomitantly there was progressive vascular disease in both the heart and the kidneys which in time would have caused these organs to decompensate.

As regards the point raised by Dr. Wilkins as to the criteria used by us to differentiate between benign and malignant nephrosclerosis, they are essentially as stated by him. The arteriolar change of benign hypertension is hyaline in type, that of malignant, hyperplastic. In this case, as is frequently found in the borderline group between ages of 45 and 65, both types of arteriolosclerosis are present and our interpretation of these findings is that the hypertension, although benign to start with, terminally developed a malignant phase. In our opinion, benign and malignant nephrosclerosis are different phases of the same disease process and frequently evidence of both phases is found in the kidneys from a single individual.

## Method for Estimating the Week of Pregnancy

The duration of pregnancy may be determined by means of a blood test recently reported by Ernest W. Page (*Science*, March 14, 1947). The method is based upon the fact that the ability of human pregnancy plasma to inactivate pitocin increases more than a thousandfold from the time of conception until term.

A sample of fresh oxalated blood is incubated with commercial pitocin and saline and samples are removed at various times for bio-assay of the residual

pitocin. The procedure in its present form requires more time and skill than a Friedman or Aschheim-Zondek test, but gives an estimate of the duration of pregnancy up to the 16-week stage with an accuracy of plus or minus five days. The accuracy of the method is not nearly as great during the last half of pregnancy, but there are already available reasonably good criteria for that period in the size, activity and osseous development of the fetus.

*A careful study of a group of patients having essential hypertension with classification from a prognostic viewpoint. The results of medical and surgical treatment are compared objectively.*

## Essential Hypertension: Prognosis and Comparison of Medical and Surgical Treatments\*

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Our opinions in regard to essential hypertension are based on a careful review of 1,072 records of patients seen by us personally. Since a single observation, however detailed, gives but a moment in the course of this condition for the given individual, we have excluded those recently seen or briefly followed (less than a year). We have excluded also those with incomplete data, those in whom classification or diagnosis is uncertain, patients with transient nervous hypertension, and patients with definite glomerulonephritis. A few patients with past histories suggesting acute or subacute glomerulonephritis remote in time but now with all the characteristics of essential hypertension are included.

There remain 646 subjects of our observations. These observations comprise a careful history, a thorough physical examination, routine blood and urine examinations, a fractional intravenous phenolsulfonphthalein test, a urine concentration test, occasionally a detailed urography, a routine orthodiagram or seven-foot x-ray film of the heart and an electrocardiogram. These examinations have been made, as a rule, at the initial visit and at approximately yearly intervals thereafter.

### CLASSIFICATION OF PATIENTS

We have found it useful to classify our patients according to organic changes in so far as they are revealed by our methods of study in the three vital areas, namely, the head, the heart, and the kidneys. The patient is graded I, mild; II, moderate; III, severe, according to the most marked manifestation of organic change in whichever area it is recognized. Patients with papilledema are graded IV.

\* From the Medical and Surgical Services and the Committee on Research in Diseases of the Autonomic Nervous System of the Massachusetts General Hospital, Boston, Mass. Read before the Mahoning County Medical Society, Youngstown, Ohio, November 19, 1946.

TABLE 1  
*Incidence and Degree of Organic Change (in per cent)  
Indicated by Clinical Examination*

	GROUP I	GROUP II	GROUP III	GROUP IV
FUNDI				
O	49	10	8	
I	51	15	14	
II		75	41	
III			37	
IV				100
HEART				
O	70	17	7	7
I	30	58	43	55
II		25	28	22
III			22	16
Coronary Disease	0.5	4	22	4
Cong. Heart Failure		1	20	26
Cerebral Accident		1	20	26
KIDNEY				
Normal	82	60	41	9
Definite Change	18	40	59	91

Table 1 shows the percentage distribution of the different degrees of organic changes in the four groups graded I mild, II moderate, and III severe. Grade IV is malignant hypertension.

Two hundred and eleven patients are graded I. They have (or had when first seen) minimal or no organic change. The eye grounds show at the most narrowing of the arterioles (51 per cent). No distinction is made by us in degree of narrowing. Even the most marked degree of narrowing is considered grade I provided there are no other retinal changes. In almost half (49 per cent) of the grade I patients the eye grounds are absolutely negative. The heart shows no change in 70 per cent. Thirty per cent show some, though slight, abnormality of the heart; usually prominence in the region of the left ventricle or slight

measurable (1 cm.) enlargement on physical examination. None have anginal or congestive heart failure. No abnormality of the kidneys or kidney function is apparent in 82 per cent of the grade I cases. Slight albuminuria with or without occasional casts in the sediment, but no impairment of function by qualitative tests is present in 18 per cent.

One hundred and forty-one patients are graded II chiefly because of more marked organic changes in the fundi as indicated by definite arteriovenous compression and/or wide arteriolar light reflex with or without marked tortuosity. This was present in 75 per cent. The remaining 25 per cent are graded II because the heart shows a greater degree of cardiac enlargement than noted in group I (but no actual or impending heart failure) the fundi being normal (10 per cent) or showing grade I changes—namely, narrowing (15 per cent). Some renal change is noted in 40 per cent occasionally with slight impairment of function. The kidneys are normal in 60 per cent.

Two hundred and thirty-seven patients are graded III because of marked organic change in one or more of the vital areas: Exudate and/or hemorrhages in the fundi or evidence of a cerebral accident; actual or impending anginal or congestive heart failure; marked renal impairment by function tests or marked abnormalities in the urinary sediment (a few). The fundi are graded III (i.e., exudate and/or hemorrhages) in 37 per cent. Arteriovenous compression and/or wide light reflex and caliber changes only are present in 41 per cent. The fundi show only arteriolar narrowing in 14 per cent. The fundi are normal in 8 per cent. Cerebral accidents have occurred in 20 per cent. Actual or impending congestive cardiac failure is found in 20 per cent, coronary insufficiency in 22 per cent. More or less evidence of renal impairment is present in 59 per cent.

Fifty-seven patients are graded IV primarily because of papilledema usually but not invariably associated with exudate and hemorrhages in the eye grounds always with marked narrowing of the arterioles. Slight enlargement of the heart is present in 55 per cent, moderate enlargement but no failure in 22 per cent, actual or impending heart failure in 16 per cent. Renal impairment usually severe is present in 91 per cent, actual renal failure (uremia), with nitrogen retention is present in 30 per cent when first seen.

This simple classification, essentially the same as that of Keith, Wagner and Barker,<sup>1</sup> is one of convenience since the factors causing the varying localizations and degree of pathologic change are not known. The fact that a grade I or grade II patient suffers a coronary thrombosis, begins to show coronary insuffi-

ciency or congestive failure, or has a cerebral accident, represents development of the disease process or demonstrates how poorly the outward signs are correlated with the inward state in a certain percentage of patients and reminds us that several observations over a period of time are required to classify a given patient with reasonable accuracy.

We find mild grade I hypertension according to our definition with minimal or no organic change at all ages but the highest incidence is in the fifth decade (age 40 to 49 inclusive). The highest age incidence of grade II hypertension with pathologic localizations estimated as moderate falls one decade later, namely, 50 to 59. No patients in this group are under 20 and only one under 30. Of patients graded III because of marked pathologic changes the largest number are, as in group II, in the sixth decade. The greatest incidence of patients graded IV in respect to age, like group I, fall in the fifth decade, 40 to 49 years inclusive.

The sex distributions: In grade I there are almost three females to one male (71 and 29 per cent); grade II has two to one (females 67 per cent and males 33 per cent); in grade III the sex incidence is almost equal, with females 54 per cent and males 46 per cent; grade IV shows definitely fewer females, namely, 41 per cent with males 59 per cent. Clearly the disease is more benign in females.

A prime characteristic of essential hypertension is the variability of the blood pressure and especially its variability upward in response to pressor stimuli. In Table 2 is shown the percentage distribution of

TABLE 2  
*Maximum Levels and Variability of the Blood Pressure  
(in per cent)*

	GROUP I	GROUP II	GROUP III	GROUP IV
Max. Systolic (mm. Hg)				
over 220	14	65	63	64
220 to 180	48	31	30	30
less than 180	38	4	7	6
Max. Diastolic (mm. Hg)				
over 140	12	55	59	59
140 to 120	45	33	24	24
less than 120	43	12	17	17
Patients Showing Occasional Return to Normal Levels	23	11	8	8
Character of Hypertension				
Marked variability	93	48	67	75
Relatively fixed B.P. levels	0	43	27	25
Wide pulse pressure with low diastolic (art.-scler. or senile)	7	9	6	0

maximum levels, the number in each group which fell to normal at some time while under observation and the percentage of each group with very marked variability and those with relatively fixed levels of the blood pressure. A small percentage in each group showed a "wide-pulse-pressure" type of hypertension with a normal or slightly elevated diastolic and a much more elevated systolic. These patients were almost always in the older age ranges with large-vessel sclerosis and no notable pathologic change other than those normal for their age. Patients with transient nervous systolic hypertension but with normal diastolic pressures were in general excluded as not true essential hypertension.

Table 3 shows the incidence of possible etiologic, participating or precipitating factors. Three-fourths of patients with essential hypertension have a family history of degenerative vascular disease. The slightly lower incidence in grade IV may be accounted for by the smaller number (57) in this group. The one to

TABLE 3  
*Possible Etiologic Factors*  
(in per cent)

	GROUP I	GROUP II	GROUP III	GROUP IV
Degree of Congenital Predisposition (Family history of degenerative Vasc. Dis.)				
0	22	26	24	33
+	38	35	29	25
++	28	23	32	34
+++	9	11	12	4
++++	3	5	3	4
	100	100	100	100
Obesity				
0	49	29	35	50
+	51	71	65	50
	100	100	100	100
Nervousness				
0	26	27	34	27
+	74	73	66	73
	100	100	100	100
Endocrine (Female)				
Total per cent	65.6	69	78.7	90
Menopause	27.5	20	40	36.8
Pregnancy	15.5	13	13	36.8
Local Renal Fault	6.5	7	4	22
Intravenous Urography				
Number studied	55	34	50	20
Number abnormal	19	9	25	14
Per cent	35	26	50	70

four plus indicates the number of siblings and forebears having degenerative vascular disease. A very marked family predisposition (three or four plus) is not found in high percentage in any group. A rather marked preponderance of obesity occurs in grade II moderate, and grade III late benign essential hypertension. Complaints of nervousness, tension, anxiety are common but no more so than patients with other diseases.<sup>2</sup> Abnormality of periods, pelvic operations, menopause, abnormal pregnancies among females are grouped as "endocrine" abnormalities together with a very few clear-cut pituitary or adrenal syndromes, the total percentage incidence (66 to 90 per cent) being high. The local renal fault (calculus disease, atrophic kidney, pyelitis or pyelonephritis, hydronephrosis, anatomic deformity of pelvis or ureters with stasis is present in a small percentage of the total in groups I to III and in a quarter of group IV. Detailed intravenous urography in 159 of this series verified the presence of some abnormal findings in 14 of the 20 cases of group IV malignant hypertension so studied, but confirmed a suspicion in half or less of the others so studied. Our experience with intravenous pyelography in essential hypertension has been reported.<sup>3</sup>

Table 4 shows the follow-up data at a given moment on this series, the data being up to date in one-half.† Certain general and tentative trends may be noted with confidence. In group IV malignant hypertension the duration of known hypertension is relatively short and early death almost certain. In groups II and III 50 per cent of the living have had known hypertension six years or longer. The slightly smaller percentage (42 per cent) having lived with hypertension as long in group I is accounted for by their younger ages. Nine to 16 per cent of patients in these three groups have had known hypertension for 15 or more years. The mortality at the moment of follow-up is progressively higher, from 6 per cent in group I to 36 per cent in group III and 80 per cent in group IV. The over-all mortality for the whole series is 30 per cent.

Some details of the deaths are of interest. Of the six known deaths in group I, two were in patients over age 70, each with mild wide-pulse-pressure hyper-

† It is considered very important statistically to note the percentage actually followed of the total number of patients seen. The study of Keith et al.<sup>1</sup> was based on 219 patients, was overbalanced by the disproportionate number of malignant cases. What percentage of total cases seen by them is represented by the actual cases followed is not noted. There is a tendency for both the severest and the mildest cases to select themselves for follow-up since the worst die under observation and the best may ascribe their good fortune to the efforts of the doctor and therefore keep in touch with him.

TABLE 4

*Known Duration of Hypertension and Mortality*

	GROUP I	GROUP II	GROUP III	GROUP IV	TOTAL
Total patients	211	141	237	57	646
Followed to date or death	100	58	111	47	316
Per cent follow up	47	41	47	82	49
Number of living	94	48	71	9	222
Years of known hyper- tension (per cent of living)					
1 to 3	27	10	25	89	
3 to 6	31	35	25	11	
6 to 10	21	30	19		
10 to 15	12	12	15		
15 to 20	6	8	9		
20 to 25	3	0	6		
25 to 30		5	1		
Number dead	6	10	40	38	94
Mortality per cent	6	17	36	80	30

tension associated by us with large-vessel sclerosis. The deaths were due to a probable coronary thrombosis in the one and to pneumonia in the other, and in each case death was attributable more to senility than to hypertension. The third death occurred in a male aged 60 after gastric resection for a bleeding duodenal ulcer. Severe coronary sclerosis not recognized antemortem, though searched for, was found. Another patient 53 years old with an apparently mild hypertension died of an intercurrent infection (streptococcus meningitis following acute otitis media). The fifth death occurred in a woman of 50 following a fall in her bathtub during an alcoholic debauch and may have been due to either subdural hematoma or a cerebral accident. There was no autopsy. The only death under 50 followed multiple nephrostomies for stone and infection in a man of 35 who had developed mild hypertension coincident to the progressive metabolic and infectious disorder of his kidneys.

Of the ten patients in group II known to have died, three died of cancer, two of cerebral accidents, two of "heart attacks" (exact data unknown). In three the cause of death is not known. Only one death occurred under 50 years of age.

Forty patients in group III or the late stage of essential hypertension are dead—18 per cent died of coronary thrombosis, 10 per cent of uremia, 28 per cent of cerebral vascular accidents, 2 per cent of bronchopneumonia, 2 per cent of generalized arteriosclerosis, 8 per cent of congestive cardiac failure, 1 per cent of multiple peripheral embolism with gangrene of both legs. In the remaining patients (approximately a third) the cause of death is unknown. Fifty per

cent had had known hypertension for from one to six years, a third from six to fifteen years, 25 per cent from ten to twenty years, and 7 per cent twenty years or more. Almost three-fourths (74 per cent) of these died at over 50 years of age.

Thirty-eight of the 49 patients in group IV, who have been followed are dead. The cause of death was uremia in 13 patients, congestive heart failure in four, cerebral accident in four. One died a few days after nephrectomy; one had paraganglioma of the adrenal and died during a hypertensive crisis. Fifteen others are known to be dead but the exact cause of death is not known to us. There are ten patients in this group whose exact status is not known to us.

The so-called late stage of benign essential hypertension, grade III, contains the average patient with this disease and its complications at middle life and beyond. Data seemed to be sufficient in 226 of the 237 to reach some conclusion in regard to the origin and progress of their condition. In Table 5 is shown

TABLE 5

*Late Grade III Hypertension—226 Patients*

Advance from mild grade I to late grade III	19%
Old-age hypertension, incidental	17%
Onset hypertension at middle age with cerebral, coronary heart disease or chronic vascular nephritis	24%
Precocious sclerosis in young adults	10%
Unclassified	23%

the result of our review. Nineteen per cent appeared clearly to have developed from mild variable grade I to the late stage of the disease. In 17 per cent the hypertension seemed to be incidental and the factor of old age and its concomitants (general, cerebral, or coronary sclerosis) the more important. Approximately one-fourth of these patients came under observation as the result of a cerebral or coronary accident or the routine discovery of signs of chronic vascular nephritis at middle life. Often these patients had not had an insurance examination or other physical examination for a number of years so that the pre-existence of hypertension could not always be excluded positively. Nevertheless the condition symptomatically appeared fairly definitely to have begun at middle life. In 10 per cent, all young adults, the patients came under observation as a result of symptoms or signs deriving from precocious arterial or arteriolar sclerosis, our guess being that the hypertension was secondary to this widespread condition. In spite of all data and adequate observation classification from this point of view was doubtful or uncertain in 23 per cent.

## EFFECT OF MEDICAL THERAPY ON BLOOD PRESSURE

In our therapy we have tried always to obey first and foremost the hippocratic injunction to do no harm. After a complete history and physical examination, as encouraging an attitude as possible is taken; not superficial blanket reassurance, which these suggestable patients resist but a reasoned explanation of the present status and an earnest persuasion that the uncertainty is not how badly but how well they may do. Doubt is instilled about the bad prognosis with which they have been saddled or with which they have saddled themselves. Sometimes a detailed personality review is done and an attempt made by direction, advice and persuasion to readjust their attitudes toward their life situation. Finally all other details of the therapeutic outline are accompanied by as much favorable suggestion as possible.

At least nine hours in bed and, when possible, daytime rest together with the appropriate amount of graded exercise, often in the form of walks, is given. Simple sedatives are used in the form of phenobarbital usually 16 mg. (gr.  $\frac{1}{4}$ ) four times daily, often with tincture of belladonna for associated irritability of the gastro-intestinal tract. Digitalis or the so-called coronary dilating drugs are prescribed when indicated by actual or impending congestive or coronary heart failure. The diet is low in cholesterol, chiefly limiting fats, together with high amounts of protein provided renal failure is not present. Formerly salt was limited to a small amount used in cooking, only occasionally was a strict low-sodium diet prescribed. More recently we have been employing a strict low-sodium diet more often and on occasion a rice diet when that commodity is readily available. As yet, we cannot report definitely our experience on the effectiveness of these latter diets. Care is taken in prescribing the regimen, always to avoid unfavorable suggestions in obtaining co-operation in treatment, and never to frighten the patient into compliance.

In the course of the first few weeks to months of treatment, commonly after the first visit, a fall in the blood pressure is noted. In nearly a half (40 per cent) a fall of 10 to 50 mm. of Hg systolic and 10 to 30 mm. of Hg diastolic will be noted.<sup>4</sup> Changes in the life situation, however, may make as notable changes either favorable or unfavorable. Transient return to normal, as noted above, occurs in 23 per cent of grade I, in 11 per cent of grade II, and in 8 per cent each of grades III and IV. Therapeutic efforts such as outlined rarely result in sustained return of the blood pressure to normal levels.

After an initial period on the above outline a certain number of patients have been given potassium sulfocyanate. One hundred of these treated for varying periods during five years have been reviewed.<sup>4</sup> Excellent results (fall to below 150 mm. of Hg systolic and 100 mm. of Hg diastolic) were obtained in 12 per cent, while a sustained fall of 30 to 50 mm. of Hg systolic and 20 to 30 mm. of Hg diastolic (though not to near normal levels) was obtained in an additional 16 per cent. Thus in a total of 28 per cent a definite hypotensive action was shown in addition to any fall in the blood pressure resulting from psychotherapy, rest, diet, and sedatives.

On conscientiously taking stock of our medical efforts from time to time we conclude as heretofore<sup>5</sup> that symptomatic relief can be obtained in a very high percentage of the mild (90 per cent) and moderate (75 per cent) and in quite a satisfactory percentage (46 per cent) of the group of patients with late benign essential hypertension. Symptomatic relief in malignant hypertension while sometimes obtained is brief. The level of the blood pressure varies widely and except for nervous hypertension (transiently at levels above accepted limits) persistently normal or near normal levels are infrequently obtained by psychotherapeutic or other medical measures. We have followed, therefore, with lively interest the blood pressure levels of our patients who have been submitted to sympathectomy.

## EFFECTIVENESS OF SURGICAL THERAPY IN REDUCING THE BLOOD PRESSURE

It has seemed to us that the final criterion in judging the effectiveness of therapy in essential hypertension is whether or not the blood pressure is reduced to normal and maintained there. This is a rare outcome indeed. Yet so variable is the blood pressure level, responsive both favorably and unfavorably to changes in the patient's life situation, to the patient's doctor, to methods of treatment and to the encouraging or discouraging suggestions associated with these that we have measured success by a persistent return of blood pressure to normal or near normal, namely, 150 mm. of Hg systolic and 110 diastolic or lower.

After over four years' experience with dorsal sympathectomy in 74 patients, 9 patients or 12 per cent by this criterion were benefited. These were chiefly patients graded I or II or patients at older ages with variable hypertension, the precise grading being undetermined. Previous to this time, Dr. R. H. Smithwick had suggested that a more extensive operation which would more certainly denervate the kidneys,

adrenals and splanchnic bed, would minimize the possibility of nerve-regeneration and that consequently a larger proportion of patients might be benefited. This prediction seemed to be realized in that of 29 patients submitted to dorsolumbar sympathectomy 20 or nearly 70 per cent, followed for a few months up to two years, were impressively benefited in respect to the blood pressure level, and for the first time patients with grades III and IV hypertension received help.

	GRADE HYP	NO OF PAT.	SEX M F	AV. AGE ONSET OF HYP	KNOWN DURATION HYP	AVERAGE FOLLOW UP	PERCENTAGE FALL TO 150/110 OR LESS	B P UNCHANGED OR WORSE	
DORSO-LUMBAR SYMPATHECTOMY	I	12	3	9	276	3 YRS 6 MOS	2 YRS 7 MOS	83%	17%
MEDICAL REGIME	I	26	9	17	319	6 YRS 1 MO	2 YRS 4 MOS	27%	73%
DORSO-LUMBAR SYMPATHECTOMY	II	7	1	6	27	6 YRS 7 MOS	8 MOS	70%	30%
MEDICAL REGIME	II	7	2	5	34	6 YRS	2 YRS 1 MO	14%	86%
DORSO LUMBAR SYMPATHECTOMY	III	18	9	9	359	5 YRS	1 YR 1 MO	22%	78%
MEDICAL REGIME	III	10	5	5	406	9 YRS 1 MO	3 YRS 5 MOS	10%	90%
DORSO-LUMBAR SYMPATHECTOMY	IV	12	8	4	34	3 YRS	1 YR	40% (57%)	60% (43%)
MEDICAL REGIME	IV	PATIENTS WITH MALIGN HYP IF NOT IN FRANK HEART OR RENAL FAILURE WERE OPERATED OTHERWISE THOSE SEEN HAVE DIED UNDER OBSERVATION OR HAVE BEEN LOST AND ARE PRESUMED DEAD							

FIG. 1. Effect of dorsolumbar sympathectomy on level of the blood pressure compared to that of medical regime.

In 1941 results of the more extensive operation were reviewed and compared with the effectiveness of medical regime in closely matched cases (Fig. 1). It was apparent that surgery was definitely more effective in persistently lowering the blood pressure to normal or near normal levels, and that the effectiveness of the operation was especially notable in grades I, II and IV. The suspicion was appearing that persistence of the effect could not be relied on since the over-all beneficial effect up to three years was now 53 per cent. This was confirmed in 1943 when the percentage of normal or near normal postoperative blood pressures in 101 patients followed one to four years was somewhat less than 40 per cent. At the present time, of 68 patients followed more than three years after operation about 25 per cent have normal or near normal blood pressures, 30 per cent are dead and 45 per cent are again or have remained hypertensive.

Three-fourths of the patients, impressively benefited for three or more years, were graded I or II, i.e., those with minimal or only moderated organic change, but there are three patients who had undoubted malignant hypertension who now have normal or near normal blood pressures; one over three years, the other two slightly less and slightly over five years after operation. Furthermore, it is apparent that benefit may be conferred by operation even though hypertensive levels persist since there are two patients who

had malignant hypertension, one more than three years, the other nearly five years ago when operated upon, who are alive and working without symptoms. Their lives have undoubtedly been prolonged, and they have been afforded considerable respite from their disease.

Those patients who are more likely to obtain the best effect on the level of the blood pressure from operation are female, are under 40 years of age, and have a variable blood pressure which falls to near normal on bed rest. In the most vasospastic type of hypertension, even though severe, namely, malignant or grade IV hypertension, the operation may be brilliantly successful. No test is sufficiently accurate to predict certainly success or failure.

Marked impairment or failure of renal function is a contraindication to operation. Frank heart failure is considered very unfavorable. Patients over 50 and in general those with clinical evidence of irreversible diffuse arteriolar disease do not receive striking benefit. Certain females at the menopause with extremely variable hypertension and occasional crises may be helped very much by operation.

Of the 21 patients in this series who have died, three may be considered operative deaths. They were in very poor condition, and we know now that they could not have been helped. At the present time the mortality is two per cent or less.

Dorsolumbar sympathectomy is done in two stages; with preliminary studies it requires six to ten weeks in the hospital. Basal atelectasis, pleural fluid, and the rare pneumothorax are complications usually taken care of easily. The operation is uncomfortable since it is followed by back pain and neuritis of flanks and abdomen lasting from two to four weeks, often for two months, sometimes for nine months or a year.

A major effect of the operation is relative postural hypotension. Immediately after the second stage is done, shock is considerable and requires intravenous fluids including plasma and blood and intravenous neosynephrine. This may last from 24 hours to two days or even longer. Thereafter on sitting or standing there is a sharp fall of blood pressure with rapid pulse, breathlessness and unconsciousness. This orthostatic hypotension is minimized by tight elastic binders on legs and abdomen. It is relieved by muscular action (walking). Tolerance of the upright position improves in the course of the day, and this tolerance is cumulative. Usually leg bandages are not required for more than one to two months. Often the abdominal binder is helpful for a longer period. There may be some compensatory general vasoconstriction since patients have commonly noted

that the hands are colder after operation, may show Raynaud's phenomena, and two patients have had relatively mild pre-operative Raynaud's disease made worse.

The pathway of pain from the upper intestinal tract is interrupted by this operation so that motor disorders of the stomach and pylorus, even perforation or bleeding from a peptic ulcer may occur with doubtful or unclear clinical signs. There is some evidence that gastritis and peptic ulcer are made worse after sympathectomy of this kind as there is theoretical reason to suppose they would be.

The effect of operation on symptoms is notable, almost without exception relieving headache, vertigo and throbbing in the head. Patients often speak of a much "clearer" head. Prescription of operation thus will depend upon the severity of such symptoms, the effectiveness of medical measures in relieving them balanced with the disability and discomfort induced by operation. At the same time the character of the hypertension and the probable prognosis will influence the choice of physician and patient.

### CONCLUSIONS

The clinical characteristics and classification of essential hypertension are discussed in relation to prognosis.

When therapeutic effectiveness is judged by a persistent lowering of the blood pressure to normal or near normal dorsolumbar sympathectomy is twice as effective as a general medical regime plus the use of sulfocyanate, but after three years this is maintained in only 25 per cent of patients, though at least 60 per cent show some lowering of the blood pressure.

Relief of headache and throbbing of the head by dorsolumbar sympathectomy is nearly 100 per cent while general symptomatic relief by medical means varies from 90 per cent in grade I to 46 per cent in grade III, is as a rule only temporary and in a smaller proportion with malignant grade IV hypertension.

Sympathectomy at this time is regarded as the treatment of choice in malignant hypertension if renal impairment is not marked, and there is no frank congestive heart failure.

Operation may be offered to those patients with variable benign hypertension without evidence of diffuse irreversible arteriolar disease, whose blood pressures by interval observations appear to be growing worse.

We are reminded that in many cases, perhaps in a majority, essential hypertension is compatible with a long and active life; often it is not accompanied by symptoms for many years.

### BIBLIOGRAPHY

1. Keith, N. M., H. P. Wagner, and N. W. Barker: Some different types of essential hypertension: their course and prognosis, *Am. J. Med. Sc.*, 197:332 (Mar.) 1939.
2. Palmer, R. S.: Etiologic factors in essential hypertension, *New England J. Med.*, 205:1233 (Dec. 24) 1931.
3. Palmer, R. S., R. Chute, N. L. Crone, and B. Castleman: The renal factor in continued arterial hypertension not due to glomerulonephritis, as revealed by intravenous pyelography, *New England J. Med.*, 223:165, 1940.
4. Fanson, E., D. Kinsey, and R. S. Palmer: Potassium sulfocyanate therapy in essential hypertension, *New England J. Med.*, 229:540 (Sept. 30) 1943.
5. Palmer, R. S.: The efficacy of medical treatment in essential hypertension, *New England J. Med.*, 215:569 (Sept. 24) 1936.

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### Injectons without Needles

The observation that the extremely fine high pressure oil jets which are used in diesel engines are capable of piercing the human skin has led to the development of an instrument which uses this principle to inject medicaments subcutaneously. The instrument was designed and developed by a diesel engineer and has been tested by Dr. Frank H. Figge of the Department of Anatomy, University of Maryland Medical School. Dr. Figge reported to the American Association of Anatomists in April that with the new device they had injected oil solutions, aqueous solutions and colloidal suspensions into cadavers and living subjects who felt practically no pain. The sterile material for injection is placed within a metal ampule which is then closed with a rubber plug. This entire sterile unit is enclosed in an aluminum container to avoid

contamination before use. Before using, the ampule is locked in the injecting instrument and the outer container removed. In the rounded tip of the ampule there is a hole 0.003 inch in diameter. When the high tension spring in the instrument is released it pushes the rubber plug into the ampule and forces the liquid under very high pressure out of the tiny hole as a high velocity fine bore jet. By adjusting the strength of the spring the depth to which the injection penetrates can be controlled. It is even possible to inject muscles which lie close to the skin.

The new device, tentatively called the Sub-Q-Jet, should prove of great practical value to pediatricians and to those persons who are required to take routine injections with insulin, penicillin and other drugs.



# EDITORIAL . . .

## The Patient and the Doctor\*

LESTER J. EVANS, M.D.

What does the patient want from medicine and from the doctor? This is a question doctors do not ask as often as they might well do.

What the patient wants, consciously or unconsciously, can be simply stated: He wants to be understood. It all seems so obvious that the patient wants to be understood. Yet, some of the very things we do or the way in which we do them in the teaching and practice of medicine have the effect of creating a sort of barrier between the doctor and the patient. The proficient use of a diagnostic or therapeutic instrument may become an end in itself instead of a means to an end, or the fascination with the inner workings of a cell or an organ may cause us to forget where that cell or organ came from. We are so anxious to make what we call a scientific diagnosis that we often ply the patient with question after question and test after test until the patient has little opportunity to tell us what he knows about himself—and he knows a lot. It has been said, facetiously I am sure, that given the chance to talk 75 per cent of the patients would make the diagnosis for us. Whatever the truth in the assertion, the fact remains that the patient has a lot to tell. The skilled physician, the one whose orientation in medicine is toward the human being who is sick as well as toward the disease, needs this information which the patient can give him, in order to make a truly scientific diagnosis; but, to be able to do this the doctor must learn to know and understand his patient.

Who is the patient? He is a person, a human being, but also an animal organism—a biologic unit living in a highly complex social structure. Thus his life is governed by social customs and demands and by those biologic laws which we all learn but may lose sight of when we become involved in the minutiae of our medical work. This patient, as a socio-biologic

entity, comes into the world endowed with certain capacities and potentialities, physical, physiologic, and psychologic. He grows and matures and is healthy if an equilibrium is maintained among these inherent forces and between them and the external or environmental forces to which he is exposed. The patient's fevers, anxieties, rashes, altered blood chemistry, lumps, or aches and pains are just signs of disturbed equilibria due to causes which may be immediate or may reach far back along the path the patient has travelled to reach the point at which the doctor sees him.

Two questions thus arise: How can the doctor learn to know more of the life pattern of the human organism generally? What knowledge and skill must he have—or get—in order to understand and to interpret the problems of the particular patient at any given time. Space does not permit me to mention all of the steps in this direction which may be taken. I should like, however, to dwell briefly on a few of them. They are preventive, social and environmental medicine, and psychiatry.

If we really believe that we can and should prevent disease or keep the patient in equilibrium within himself and with his environment there is much to do beyond the point we have now reached in preventive medicine. Many diseases can be prevented through specific community and individual measures. The handicaps and disturbances caused by many so-called nonpreventable diseases can be lessened. In many instances life can be lengthened. There are, nevertheless, a large group of conditions about which we can do nothing in the way of prevention until we know more about the basic physiology, biochemistry, and over-all function and life of the human organism. It is at this point that the basic sciences are so vital to clinical preventive medicine.

Because interest in clinical preventive medicine comes in part from public health, which is concerned

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\* Adapted from a talk given before a dinner meeting of lay and professional friends of the Long Island College of Medicine, December 10, 1946.

with the community factors of health, we are all more conscious of the environments in which we live. When we begin to examine the environment we find that it consists of many aspects which bear upon the individual's health. Exposure to infectious disease is one; housing is another; the working conditions which exist in the shop or factory, and the kind and quality of food are others. But one's human associates are also a part of that environment. What we get from and what we give to the people we live with, the people we work with, or the people we play with are as much a part of our process of living as the food and water we consume or the infectious diseases we are exposed to.

It was not until the development of modern psychiatry that we have become fully aware of the significance of the fact that the people we know are so important a part of our world. Psychiatry is the science which deals with human emotions and interpersonal relationships. It explains why the people we know, including our doctor, are so important to us. We understand now how our emotional development is nourished or stifled by our human environment.

The emotional and intellectual life and the physical life of an individual are inseparable. We have just one body, one set of organs, one system of physiologic functions to give expression to all of our behavior whether physical or emotional. Thus it is easy to understand why there should be what is now popularly called psychosomatic disease. It is an illness in which abnormal emotional behavior is responsible for the disturbance in our over-all functioning. In psychosomatic disease there may be many of the same symptoms which are found in so-called physical disease. Even though the mechanism of the psychosomatic illness process cannot be examined fully with our present tools of scientific study—the microscope, the biochemical test-tube, the physiologic analysis—we know the emotional components are just as real as those things which we can see and feel.

What does all this mean to the patient who wants to be understood by his doctor? Perhaps I can make it clear by tracing the steps which are necessary if the

physician is to be capable of understanding people. He must first know what the human organism is—how it grows, matures and ages, and how it functions and behaves at all stages of the life span. In the laboratories of the medical sciences he must have learned what the parts of the body are and how they function. He must have discovered that each part and each function is dependent on or related to all other parts and functions. He has learned that the emotional growth is as definite and as purposeful as the physical. Sensing this, he builds for himself a concept of over-all function and behavior—a concept which he must never lose sight of during his medical career, whether he is a general physician, a specialist, or a medical scientist. Next he must know about the abnormalities of human function and behavior; and develop broad concepts of health and disease. He can only do this by knowing the human organism in relation to its environment, because the human being does not grow and develop, remain well, or become sick in a vacuum.

As the doctor goes about his practice he sees people in trouble. If he is wise, he learns how to listen to them, how to talk to them, how to draw them out, how to examine them. He views them in terms of their past development and performance and inquires specifically into their way of living. He must know about their human relationships. In making a diagnosis he draws on his own observations and laboratory aids. He studies the ways of restoring the patient to a state of physical, physiologic, and psychologic equilibrium—not one or another, but all. He learns how to prevent some diseases and what new knowledge is needed to prevent others. And finally something else happens. His patients seem more at ease with him and he with them. He finds the stories of their lives more meaningful. He is able to act freely with objective kindness and understanding. As he comes to sense the true patient-physician relationship he is able to give his patients what they really need and so to practice medicine with more benefit to them and more satisfaction to himself.

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*The author believes that sinusitis is an important factor in the clinical manifestations of a variety of allergic states. He gives evidence to establish this point as well as indicate the successful results of his recommended treatment of the sinusitis.*

## Sinusitis and Allergic Diseases \*

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Sinusitis as a recognized disease is an old disease. The maxillary sinus was known to the anatomist, Vesalius, in 1538. The name, antrum, was given to this sinus by an English physician, Nathaniel Highmore, in 1651. He described an infection of the maxillary sinus which developed subsequent to the extraction of a tooth. Allergy on the other hand is a more recently recognized factor in disease. Elliotson in 1831 first suggested pollens as a cause of hay fever. However, it was not until 1873 that Blackley reproduced hay fever and asthma by applying pollen to his nose, eyes and mouth.

According to Adams,<sup>1</sup> Herck of Freiberg in 1844 first recognized the importance of sinusitis as a cause of asthma. However, it was not until 1871 that Vololini<sup>2</sup> showed the effect of sinus surgery on asthma when he reported a case of asthma in whom a cure followed polypectomy. In recent years the importance of sinusitis as an etiologic factor in allergic diseases has become a question of controversy. Today we know that sinusitis plays an important part in the treatment of asthma, urticaria, angioneurotic edema, eczema, vasomotor rhinitis and hay fever. In some of these diseases it is a primary factor while in others it is a secondary but definitely important factor.

Sinusitis has been discredited as a cause of allergic diseases because of the oft reported poor results obtained by the medical or surgical treatment of sinusitis. I think this is due, first, to faulty diagnosis of the sinusitis as an etiologic factor in the allergic disease and, second, to inadequate treatment, especially surgical treatment, of the sinusitis. A patient whose urticaria is due to the ingestion of certain foods or contact exposure, or a patient whose asthma is due to pollens, house dust, danders or foods will not be benefited by an operation on the sinuses.

To discuss the topic in hand intelligently it is necessary to remember these facts: namely, that certain allergic manifestations are of the skin-sensitive type

and others are of the nonsensitive or infective type. The first type is diagnosed by the positive skin tests, patch tests or elimination diets. The second group is negative on skin testing and the presence of disease in the upper respiratory tract as well as its influence on the allergic disease can be demonstrated. In addition to the skin-sensitive and the infective types we have the combined type, that is, the patient may show positive skin reactions and also the presence and influence of foci of infection.

In discussing the importance of sinusitis in allergic diseases it is necessary to know the pathology, bacteriology and diagnosis of the sinusitis. There are allergic manifestations in almost 100 per cent of the hyperplastic type in its primary stage. In other words, it is a thickened nonpurulent type of membrane pathology. The membrane is often an eighth to a quarter of an inch thick, infolding and showing under the microscope a desquamation of the cilia, a marked thickening of the basement membrane and, in the tunica propria, edema, glandular hyperplasia, proliferation of the connective tissue and eosinophilic cell preponderance with some round and plasma cell infiltration. Neutrophils are not frequent unless there is a secondary infection. Polyposis and cystic or mucocoele formation may or may not be frequent. However, they are the most frequent form of pathology of the antrum in urticaria and angioneurotic edema. Kelley<sup>3</sup> in a survey of 100 cases of asthma found polyps present in 26 per cent. In my observation in the patients who have not been operated upon previously this is a little high.

These hyperplastic membranes have been cultured and 80 per cent found positive for one or more organisms.<sup>4</sup> Only one of 29 antral membranes was negative while 16 of 51 ethmoidal and sphenoidal membranes were negative. This is easily explained by the fact that the ethmoidal and sphenoidal pathology was usually mucous or cystic polyps, the contents of which are frequently sterile, the infection being in the underlying sinus membranes. Thirty-four of the positive cultures yielded a single organism. This seems important from the standpoint of the

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value of the organism as an etiologic agent in the disease. A comparison of the organisms obtained from 87 membranes with those grown from previous washings or surface cultures of the antra showed that 43.7 per cent were different from any recovered pre-operatively. In other words, a negative culture from an antrum lavage does not necessarily mean a normal or noninfected sinus. Stained sections of the tissues removed from the sinuses demonstrated very definitely the presence of bacteria in 85 per cent. Rosenow of the Mayo Clinic checked Kistner's<sup>5</sup> sinus membranes microscopically and agreed that bacteria were present frequently.

In other studies<sup>6</sup> the bacteria found were: staphylococcus, 57 per cent; *Streptococcus viridans*, 43 per cent; pneumococcus, 39 per cent; hemolytic streptococcus, 25 per cent; indifferent streptococcus, 3.7 per cent; *Micrococcus catarrhalis*, 3.7 per cent; *Bacillus proteus*, 0.9 per cent; *Bacillus coli*, 0.9 per cent; *Bacillus diphtheroid*, 0.9 per cent; negative, 4 per cent. Kistner<sup>5</sup> studied 400 sinus membranes and found streptococcus present in 94.5 per cent of his cases. Hansel,<sup>7</sup> Piness and Miller,<sup>8</sup> Ashley and Frick<sup>9</sup> and Balmer<sup>10</sup> believe these organisms are secondary invaders. However, this is not the belief of Goodale,<sup>11</sup> Kistner<sup>5</sup> or of our clinic.<sup>4</sup>

One might ask, how is the diagnosis of this hyperplastic sinusitis made? It is made by careful clinical, physical, laboratory and x-ray examinations. The history of frequent colds, stuffiness, postnasal discharge, sneezing and headaches may be present, but frequently all of these symptoms are absent. The patient may say "my nose is quite comfortable and I don't want any examination of it." The nasal examination should include anterior rhinoscopy and the use of the nasopharyngoscope. Frequently discharge and polyps posteriorly may be overlooked unless the nasopharyngoscope is used. Transillumination should be done but if this is negative the examination is not complete. Roentgenograms should be made as polyps or cysts in the antra may not be demonstrated by transillumination.

I found in some of my patients that plain x-rays were not always conclusive. In such cases I used to resort to lipiodol injection of the antra but in some patients I felt that the lipiodol obscured the pathology especially if it was a polyp protruding into the center of the antrum and in a few patients I encountered a sensitivity to iodine. I then selected umbrathor,<sup>12</sup> a 25 per cent suspension of colloidal thorium dioxide. This gave a more delicate shadow and is easier to handle by injection than lipiodol. I have injected it in at least 350 sinuses without any reaction.

The laboratory examinations include cytologic and

bacteriologic examination of the nasal and sinus secretions. In most of the patients the eosinophils predominated. This is often true also of the blood of the infective cases in whom the eosinophils may be 8 to 15 per cent. Cultures are made of the sinus washings but as stated previously a negative culture does not mean a noninfected sinus.

A thorough study for other foci of infection in the tonsils, adenoids and teeth is necessary before the examination is complete. Operations on the sinuses are frequently unsuccessful because a secondary focus is overlooked in one of these sites, especially the teeth and adenoids. A thorough general physical examination for any other possible contributing factors should be made before instituting sinus operations.

Let us discuss more specifically the relationship of sinusitis to the various manifestations of allergy.

### HAY FEVER

Sinusitis is never the cause of hay fever but it can be a very important factor in influencing the results of treatment. I have found that a flare-up of sinusitis during the hay fever season will quite often increase the nasal symptoms. This is especially true of the type of sinusitis frequently seen following swimming, or chilling as from air conditioning.

Sinusitis associated with nasal polyposis is also apt to increase the hay fever symptoms. In a study of these patients with polyps I found that asthma was about 10 per cent greater in them during the hay fever season than in the nonsinusitis patients.

The treatment of this sinusitis during the pollen season should be conservative. The irrigation of an antrum will often clear up the increased hay fever symptoms like magic. After the pollen season is over polyps should be removed and if surgery of the sinuses is indicated it should be carried out. I never operate on these patients during the pollen season because the nasal symptoms may be magnified, asthma may result and the healing is often delayed with a poor post-surgical result.

### VASOMOTOR RHINITIS

Sinusitis may be the primary cause of a vasomotor rhinitis or a secondary influencing factor. It is a secondary factor in many patients who have been tested and found sensitive to certain inhalants or foods. In these patients we often get a history of long drawn out treatment with injections and eliminations without results. They often give a history of upper respiratory infections which increase their symptoms.

The primary group is made up of the patients whose symptoms generally began after a cold. They have been tested by the allergist and found negative.

They are then examined by the otolaryngologist who says "you have no sinusitis," or, "you have only thickened membrane in the antra and that is not the cause of your trouble." Frequently these patients have had only a transillumination of the sinuses or an antral lavage but have not been x-rayed. Sinus pathology is overlooked in this group more often than in any other allergic manifestation. The use of umbrathor or lipiodol is frequently necessary to establish the diagnosis. If polyps are present in the nose the rhinoscopic examination will make the diagnosis. When they are absent the otolaryngologist will often say the condition is not an allergic rhinitis because the membranes may be very red and dull instead of being boggy, pale or grayish and watery as in the characteristic allergic type.

Our studies<sup>4,6</sup> have convinced us that these thickened membranes in the sinuses are infected and the patients have become sensitized to the bacteria or their products. In the group in which the sinusitis is the primary cause conservative treatment consisting of irrigations of the sinuses when indicated and the use of vaccines, both stock and autogenous made from the sinuses, may be used first. Quite often, however, this treatment is not very successful and we have to resort to surgical procedures. These procedures should be complete. Simple removal of the nasal polyps is not sufficient. The infected membrane in the underlying sinuses, whether ethmoidal, sphenoidal or antral, must also be removed. We usually make vaccines from these diseased membranes and the patients are continued on this treatment after the operations.

The use of benadryl, pyribenzamine and, in a few cases, anthallan, has not been very successful in these cases of infective vasomotor rhinitis. They may have been more effective in the patients who have demonstrable skin sensitizations and in whom the sinusitis is a secondary factor. This group, however, usually do well with the treatment of their sensitizations and the use of vaccines, and operations on the sinuses are not indicated as frequently.

### MIGRAINE

I have never seen a patient with true migraine in whom sinusitis was the primary cause. The attacks may be influenced by an associated sinusitis which naturally needs treatment as indicated. I think the neuralgias and the type of headaches which we often see in allergic patients are wrongly diagnosed as migraine. These "pseudo-migraine" patients are the ones who are often so enthused about their sinus treatments or operations.

### URTICARIA AND ANGIONEUROTIC EDEMA

Sinusitis as a cause of urticaria and angioneurotic edema is frequently overlooked by the internist as well as by the allergist and otolaryngologist. In my experience it is an important cause in a large number of those with chronic manifestations, especially the ones who are negative on testing and in whom elimination diets and "contact" studies produce no relief.

Fink and Gay<sup>13</sup> in a study of 170 such patients found that the group with focal infections as the cause made up the greatest number (52 patients or 30 per cent). Sinusitis was present in nine patients which I think is much lower than we found in our studies.

The form of sinusitis found most frequently in these patients consists of hyperplastic or thickened membranes, especially in the antrum, and it is often associated with polyps or cysts in the antrum. It is often difficult to diagnose by simple rhinoscopy and transillumination. It requires roentgenologic examination and occasionally the injection of umbrathor or lipiodol into the antrum.

The conservative treatment of these patients with vaccines, both stock and autogenous, may be beneficial but most of them eventually require operation. Fink and Gay<sup>13</sup> reported 74 per cent cured and 12 per cent improved in their group of 170 patients in whom foci of infection were removed. They emphasized the fact that all associated infections in the teeth and tonsils or elsewhere should be removed because a poor result may be obtained if one focus is removed and another allowed to remain. I also have observed frequently that following operations on the sinuses only temporary relief is obtained until the additional infection elsewhere, especially in the teeth and tonsils, is removed. We continue to treat our patients after operation with injections of vaccines made from the diseased tissues.

I might add that the urticaria and angioneurotic edemas secondary to sinusitis usually do not respond to the use of the new antihistaminic drugs for long.

### ECZEMA

In recent years we have come to recognize that the eczemas seen in allergic patients is frequently secondary to a sinusitis. These patients are frequently negative on skin testing both intradermal and patch and the use of elimination diets has not produced any relief. Upper respiratory infections usually exacerbate the skin lesions.

As in the case of the urticarias and the infective vasomotor rhinitis, the nasal examination is often negative and roentgenograms are necessary. This

group quite often requires the use of an opaque medium injected into the antrum to establish a diagnosis. The pathologic change is the thickened hyperplastic membrane with polyps or cysts often present.

Some of these patients may be helped by the use of vaccines but usually an operation is required. To effect a more permanent relief we also advocate the use of a vaccine made from the diseased sinus membrane after operation. If any associated infections are present, particularly in the teeth and tonsils, they should be removed. We have had excellent results especially in the younger group with such treatment.

### ASTHMA

Asthma is the one allergic manifestation that is associated very importantly with sinusitis. Many allergists and otolaryngologists are undecided whether sinusitis is the cause of asthma or asthma is the cause of sinusitis. Such allergists as Rackemann<sup>14</sup> and Gay<sup>15</sup> are undecided about the exact etiologic nature of sinusitis as a cause of asthma. We, however, are very definitely of the opinion that sinusitis may be the primary or secondary cause of asthma.

In the first part of this paper I discussed the nature of this sinusitis, the pathology, bacteriology and diagnosis so I will not go into additional detail. I want, however, to show the incidence of sinusitis in asthmatic patients and to discuss the results of the treatment of the sinusitis as far as the effect on the asthma.

The incidence of sinusitis in asthma patients as reported in the literature varies. One answer to this is the method of diagnosis of the sinusitis. If it is diagnosed by rhinoscopy alone the incidence is low. If it is diagnosed with x-rays the incidence is higher. Gottlieb<sup>16</sup> found sinusitis present in only 26 per cent of 117 patients with asthma. Kern and Schenck<sup>17</sup> after a careful study of 400 cases of asthma found that 70 per cent had clinical evidence of sinusitis and 87.5 per cent showed x-ray evidence of disease. Kelley<sup>3</sup> reported that 89 per cent of 100 patients with asthma had rhinologic and x-ray evidence of sinusitis.

The most comprehensive study of the incidence of sinusitis as a cause of asthma was reported by Cooke.<sup>18</sup> He analyzed 688 cases of asthma and found sinusitis to be the cause of the asthma in 39 per cent of 257 cases with the asthma beginning between 10 and 30 years of age; 65 per cent of 171 cases between 30 and 50 years and in 83 per cent of 42 cases after 50 years. Excluding the children in the first decade of life in whom the tonsils and adenoids and the lymphoid tissue of the pharynx are more important he found that sinusitis was the only cause of the asthma in 45 per cent of 470 patients.

It might be asked, "how frequent is asthma present

in patients with sinusitis?" Bullen<sup>19</sup> studied 400 cases of sinusitis and found that one-fourth of them had some form of nontuberculous pulmonary disease, 12.25 per cent of them had asthma, while 8.75 per cent actually had their asthma begin at the same time as their sinusitis. When one considers that the percentage of allergic disease in the general population is 10 to 15 per cent it is evident why the percentage of asthma in Bullen's group is so low because sinusitis if it is to cause asthma must occur in a person with an allergic constitutional background.

Cooke<sup>18</sup> in his study of the group of 688 cases with asthma also found that there was a positive antecedent history of allergy in 45 per cent of the entire infective group and 52 per cent of the skin sensitive group, 66 per cent of 195 cases of asthma gave an antecedent history of asthma and there were other allergic manifestations in 34 per cent.

Maxillary sinusitis is the most frequent type of sinusitis found and ethmoidal the second. Frontal sinusitis is the least frequent. In a study<sup>20</sup> of 163 patients, maxillary sinusitis was present unilaterally in 44 patients and bilaterally in 108, while ethmoidal sinusitis was present in 40 unilaterally and 98 bilaterally. This study shows how frequent the sinusitis is bilateral and I might add that pansinusitis is present in a high percentage.

We are now at the stage where we may ask, "what is the treatment of this sinusitis and what are the results?" The medical treatment, so to speak, is not very important in hyperplastic sinusitis. Irrigations are done for cultures and if there is a suppurative exacerbation the use of sulfonamide preparations and penicillin are helpful in the acute exacerbations. But for the treatment of chronic hyperplastic sinusitis they are of very little value.

The treatment of the hyperplastic sinusitis when it has reached the proper stage is operative. When I say operative I mean the complete removal of the infected tissues. A simple polypectomy or the "window" resection of the antrum seldom suffices. When removing nasal polyps the underlying infected membranes in the ethmoids or sphenoids must also be removed and the removal of the diseased membrane in the antrum requires a radical operation. Submucous resection and turbinectomy are worth very little as far as producing any permanent improvement in the asthma.

We<sup>21</sup> have always maintained that the complete operative removal of this hyperplastic membrane is necessary if a good result is to be obtained with the asthma. Gay<sup>15</sup> on his recent book on asthma has taken the same attitude.

In the previously quoted group of 163 patients with

asthma, I did an ethmoidectomy unilaterally on 34 patients and bilaterally on 91, and an unilateral Caldwell-Luc operation on 37 patients and a bilateral on 64 patients.

The reports in the literature regarding the benefits of sinus operations on asthmatic patients are variable and I might add are not too encouraging. Heatley and Crowe<sup>22</sup> in a series of 62 operative cases found 53 improved but only one case was enthusiastic enough to describe himself as cured after three years. Rackemann and Tobey<sup>14</sup> in a study of 91 cases of asthma treated surgically reported 14 per cent cured, 46 per cent improved, 31 per cent unimproved and 9 per cent dead. Weille<sup>23</sup> stated that in his group of 40 patients on whom he had operated for sinusitis only 30 per cent had a chance for relatively long continued improvement in their asthma. Schenck and Kern,<sup>24</sup> Vaughan<sup>25</sup> and Warner and McGregor<sup>26</sup> reported even less favorable results.

Gay<sup>15</sup> in his recent book on asthma analyzed 125 patients with asthma whose sinuses had been operated on at the Johns Hopkins Hospital. The longest postoperative period was 20 years and the shortest two years. Twenty-four patients (19.2 per cent) reported complete relief; 26 cases (20.8 per cent) reported infrequent attacks of asthma, occurring especially when they carelessly exposed themselves to inclement weather condition; 17 cases (13.6 per cent) reported recurring attacks but not so severe as before opera-

tion; 5 cases (4.0 per cent) reported questionable relief and 53 patients (42.4 per cent) reported no relief whatever. Unfortunately in his report Gay did not give any information as to the associated allergies in his group of poor results nor the completeness of operative removal of diseased sinus membranes. He stated, however, that 71 patients had recurring sinus symptoms subsequent to their operations. In the main these failures respecting sinusitis included the 53 (42.4 per cent) of the reported failures in asthma.

It seems to me from a study of these reports that there are reasons to explain the discouraging results. In the first place the importance of associated sensitizations is often not made clear, nor, in the second place, how completely the diseased sinus membranes were removed, that is, whether all the sinuses were operated upon or isolated ones only. We have always maintained that this critical analysis of operative results is necessary.

Since 1935 we have made six very complete studies<sup>4, 20, 21, 27</sup> of the results of sinus surgery on patients with asthma. The first study reported in 1935 included 120 cases, the longest of whom had been followed for three and one-half years postoperatively. The results of the most recent study are reported in Tables 1, 2, and 3. Our results have shown 70 per cent, or slightly less, improved in all the five previous studies and the sixth showed 69 per cent. We have not included the first six postoperative months because the results are too transitory. The effect of the anesthetic often produces a temporary relief from

TABLE 1

*Results of Surgery on the Sinuses in 200 Cases of Asthma*

POSTOPERATIVE (YEARS)	CASES	IMPROVEMENT		
		+	++	+++
½-1	18	8	8	2
1-2	23	9	8	6
2-3	18	7	6	5
3-4	24	10	9	5
4-5	17	3	9	5
5-6	11	5	1	5
6-7	7	4	3	2
7-8	8	2	6	8
8-9	17	2	4	3
9-10	22	6	5	1
10-11	9	1	0	4
11-12	16	1	7	2
12-13	15	3	3	2
13-14	8	1	2	3
14-15	6	0	2	4
15-16	6	0	3	3
16-17	2	0	1	1
Total	200	62	77	61

138 or 69%

+ Indicates slight or no improvement.  
++ Indicates definite improvement.  
+++ No asthma or a rare attack.

TABLE 2

*Results of Surgery on the Sinuses in 200 Cases of Asthma Based on the Completeness of Removal of All Diseased Tissue*

POSTOPERATIVE (YEARS)	COMPLETE SURGERY			INCOMPLETE SURGERY		
	+	++	+++	+	++	+++
½-1	4	5	1	4	3	0
1-2	6	7	5	2	2	2
2-3	0	6	3	7	0	2
3-4	5	7	3	6	1	2
4-5	3	9	5	0	1	0
5-6	3	0	4	3	0	1
6-7	3	2	1	3	0	1
7-8	0	6	5	2	0	2
8-9	0	4	3	2	0	0
9-10	2	5	1	4	0	0
10-11	1	0	3	0	0	1
11-12	1	6	2	0	1	0
12-13	1	3	1	2	0	0
13-14	1	2	3	0	0	0
14-15	0	2	4	0	0	0
15-16	0	3	3	0	0	0
16-17	0	1	1	0	0	0
	30	68	48	35	8	11

116 or 79.9%

19 or 35.2%

the asthma in some patients, while in others the removal of the infected sinus membranes may produce immediate exacerbation of the asthmatic symptoms.

TABLE 3

*Results of Surgery on the Sinuses in 200 Cases of Asthma Based on the Type of Asthma*

POSTOPERATIVE (YEARS)	INFECTIVE TYPE			COMBINED TYPE		
	+	++	+++	+	++	+++
$\frac{1}{2}$ -1	5	4	0	3	4	2
1-2	8	3	2	1	5	4
2-3	3	5	3	4	1	2
3-4	4	4	2	6	5	3
4-5	3	1	1	0	8	4
5-6	4	1	1	1	0	4
6-7	3	2	1	1	1	1
7-8	2	5	2	0	1	6
8-9	1	3	0	1	1	3
9-10	5	4	0	1	1	1
10-11	1	0	0	0	0	4
11-12	0	4	2	1	3	0
12-13	1	2	1	2	1	1
13-14	1	1	1	0	1	2
14-15	0	2	3	0	0	1
15-16	0	2	2	0	1	1
16-17	0	1	1	0	0	0
	41	44	22	21	33	39
		66 or 61%			72 or 77.4%	

I have divided the operative group for comparison, first, between the types of asthma (i.e., infective primarily or infection plus associated sensitizations) and second, between those in whom all the sinuses infected have been operated on and those in whom isolated operations or incomplete surgery has been done.

Tables 1, 2 and 3 analyze 200 patients according to the postoperative periods. The symbols +, ++ and +++ have been selected arbitrarily to designate the improvement in the asthma. One plus signifies slight improvement in asthma, no improvement or even worsening; two plus designates improvement as agreed upon by the patient and the physician; three plus no asthma or a rare attack. The improvement in the whole group is expressed as the sum total of the two plus and three plus results or 69 per cent. This is about the same as those reported in our three previously reported surveys and in Cooke's book on allergy.<sup>20</sup>

The infective group comprised 107 cases and the combined group, that is infection plus sensitizations, 93 cases. The group completely operated on comprised 146 patients and the incomplete group 54 patients. Referring to Table 2, it is obvious that the group completely operated on showed a much higher percentage of improvement (79.9 per cent), than the group incompletely operated on (35.2 per cent). I

would like to add here that 27 patients who had had a "window" resection or antrotomy showed only 40 per cent improvement with their asthma. Nineteen of these patients subsequently had a radical antrum operation and 79 per cent showed improvement with their asthma later.

It should be noted that in the group completely operated on the incidence of improvement is greater with the longer postoperative periods. I believe that this may be explained by the fact that there are secondary foci in the cervical and bronchial lymphatic glands and in the bronchial mucosa. These secondary foci heal slowly. It is possible that the patients who did well immediately after operation and remained well never had these secondary foci. On the other hand, the patients who did not do well, even as the postoperative period increased, may have lacked the capacity to overcome these foci.

Referring to Table 3, it is seen that the results are better in the combined type of asthma than in the infective type. In the former group the infection is often a secondary factor and in addition all these patients were treated with injections of the indicated allergens as well as by the elimination of the allergens when possible. I think the injections of house dust in the proper patients has helped to maintain prolonged freedom from asthma and at the same time helped to prevent the occurrence of nasal polyps. Practically all the patients in the infective and combined groups have been given injections of vaccines made from cultures of the infected sinus membranes removed at operation. In addition, all those with extranasal infections such as molds and spirochetes have been treated, and infected teeth, tonsils and adenoids have been removed.

I have also studied this entire group of patients from the standpoints of age at onset of the asthma, duration of the asthma, and age at operation. In a total of 52 patients in the three plus group only 7 (13.4 per cent) developed their asthma before 21 years of age, while in the one plus group of 64 cases there were 21 such patients (32.8 per cent). The greatest number of patients in the three plus group developed their asthma between the ages of 21 and 35 years; there was another peak from 50 to 55 years.

As far as duration of asthma is concerned, of 46 of our three plus patients practically 50 per cent had had their asthma less than five years, while an additional 25 per cent had had their asthma not more than six to ten years. Of 60 patients in the one plus group (40 per cent) had their asthma for five years or less and 60 per cent for ten years or less.

An analysis of the group from the standpoint of age at operation showed that of 46 patients in the



three plus group 76 per cent were between the ages of 31 and 50 years. Of 62 patients in the one plus group 31 per cent were between the ages of 20 and 35 years and 34 per cent between 35 and 50 years. It is interesting to note that 14 per cent of the one plus group were between 50 and 60 years of age.

### SUMMARY

An attempt has been made to show that sinusitis is an important primary or secondary factor in the etiology of the various manifestations of allergy. The pathology, bacteriology, incidence, diagnosis and treatment especially surgical of the sinus disease have been discussed.

It has been emphasized that the type of allergic disease, whether infective, or combined (infective plus sensitizations) must be determined. Furthermore, in the surgical treatment of the sinusitis the diseased membranes must be removed completely to achieve the best results.

An analysis of 200 patients with asthma whose sinuses were operated upon is presented. Sixty-nine per cent of the total group showed complete or definite relief of their asthma. The group in whom all the diseased sinus membrane was removed showed 79.9 per cent improvement, while the group in whom not all the sinuses infected were operated upon only 35.2 per cent showed relief of their asthma. The patients who had sensitizations associated with their sinus infections showed a 16.4 per cent greater improvement in their asthma.

The best results were obtained in those patients whose asthma began after 21 years of age, in whom the duration of asthma was less than five years or not over ten years, and where the age at operation was between 31 and 50 years.

In all the manifestations of allergy in which infection is a factor, any associated allergies or infections must be treated or eliminated if possible. Postoperative injections of vaccines, both stock and autogenous, have been used in most of our patients.

### BIBLIOGRAPHY

- Adam, James: *Asthma*, ed. 2, St. Louis, Mosby, 1926, p. 99.
- Voltolini, R.: *Die Anwendung der Galvanokaustik*, ed. 2, Wien, Wilhelm Brannmüller, 1871, pp. 246-250, 312.
- Kelley, S. F.: Incidence of sinusitis and nasal polyps in bronchial asthma, *Laryngoscope*, 46:692, 1936.
- Grove, R. C., and R. A. Cooke: Etiology and nature of chronic hyperplastic sinusitis, *Arch. Otol.*, 18:622, 1933.
- Kistner, F. B.: Histopathology and bacteriology of sinusitis, with comments on postoperative repair, *Arch. Otol.*, 13:224, 1931.
- Grove, R. C., and J. Brown Farrior: Chronic hyperplastic sinusitis in allergic patients, *J. Allergy*, 11:271, 1940.
- Hansel, F. K.: Nose and sinuses in allergy, *J. Allergy*, 1:43, 1929.
- Piness, G., and H. Miller: Specific protein reactions in eyes, ear, nose and throat, *Ann. Otol., Rhin., & Laryng.*, 38:691, 1929.
- Ashley, B. J., and W. V. Frick: A bacteriologic and cytologic study of the maxillary antrum in children, with a clinical study of 83 cases, *Ann. Otol., Rhin., & Laryng.*, 38:605, 1930.
- Balmer, F. B.: The relation of clinical to bacteriologic observation in normal and in diseased maxillary antrums, *Arch. Otol.*, 14:440, 1931.
- Goodale, J. L.: *Vasomotor disturbances of upper air passages and sinus disease*, *Ann. Otol., Rhin., & Laryng.*, 31:882, 1922.
- Grove, R. C., and R. A. Cooke: The use of thorium dioxide in roentgenography of the sinuses, *Am. J. Roentgenol.*, 44:680, 1940.
- Fink, A. I., and L. N. Gay: A critical review of 170 cases of urticaria and angioneurotic edema followed for a period of 2 to 10 years, *Bull. Johns Hopkins Hosp.*, 4:280, 1934.
- Rackemann, F. M., and H. G. Tobey: Studies in asthma: IV. The nose and throat in asthma, *Arch. Otol.*, 9:612, 1929.
- Gay, L. N.: *The Diagnosis and Treatment of Bronchial Asthma*, Baltimore, Williams & Wilkins, 1946.
- Gottlieb, M. J.: Relation of intranasal disease in production of bronchial asthma, *J. A. M. A.*, 85:105, 1925.
- Kern, R. A., and H. P. Schenck: Chronic paranasal sinus infection: relation to diseases of the lower respiratory tract, *Arch. Otol.*, 18:425, 1933.
- Cooke, R. A.: Infective asthma: indications of its allergic nature, *Am. J. M. Sc.*, 183:309, 1932.
- Bullen, S. S.: Incidence of asthma in 400 cases of chronic sinusitis, *J. Allergy*, 4:402, 1933.
- Cooke, R. A.: *Allergy in Theory and Practice*, Philadelphia, Saunders, 1947.
- Cooke, R. A., and R. C. Grove: Relation of asthma to sinusitis, *Arch. Int. Med.*, 56:779, 1935.
- Heatley, C. A., and S. J. Crowe: Asthma and infections of the accessory nasal sinuses: a study based on 62 cases, *Bull. Johns Hopkins Hosp.*, 34:410, 1923.
- Weille, F. L.: Studies in asthma XVIII. The surgical treatment of chronic sinusitis in asthma, *J. A. M. A.*, 100:241, 1933.
- Schenck, H. P., and R. A. Kern: An evaluation of the therapeutic effect of the Caldwell-Luc operation in bronchial asthma, *J. Allergy*, 3:296, 1932.
- Vaughan, W. T.: Some rhinologic aspects of allergy, *J. Allergy*, 4:127, 1933.
- Warner, W. P., and G. McGregor: Effect of radical antrum surgery on bronchial asthma, *J. Laryng. & Otol.*, 48:595, 1933.
- Grove, R. C.: The importance of chronic sinusitis in the treatment of bronchial asthma, *New York State J. M.*, 41:455, 1941.

# The Earlier Recognition of Minimal Aortic Insufficiency

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It is surprising how frequently cases of slight aortic insufficiency escape the attention of the medical examiner. Just as the pulmonic region has been termed the "area of romance," the aortic region might be referred to as the "area of oversight." Although the pressure of the war emergency occasionally resulted in incompleteness of examination, most of the cases to be reported here had been repeatedly missed in civilian life as well, despite a definite history of previous rheumatic infection in many cases. Twenty-four such instances came to our attention in a relatively short period of time and impressed us with the necessity of earlier diagnosis. It is the purpose of this paper to stress a simple method for the early recognition of aortic insufficiency.

## THE IMPORTANCE OF EARLIER RECOGNITION

Early recognition of any phase of rheumatic fever is of utmost importance because the disease attacks such large numbers of young adults in the services as well as in civilian life; because of its frequency following epidemic type A hemolytic streptococcal infections of the upper respiratory tract; because of the excellent response to intensive salicylate therapy which tends to shorten the disease and inhibit cardiac complications; and finally, because of the current use of sulfadiazine and other measures prophylactically. With earlier diagnosis of aortic insufficiency, the work load can be decreased and more intense application given to the avoidance of infections since exacerbations eventually result in the classical signs of increased pulse pressure and cardiac hypertrophy.

The importance of early recognition is shown by the fact that most authorities (Gibson, Broadbent, Babcock and others) arrange the valvular lesions according to gravity as follows: aortic insufficiency, mitral stenosis, aortic stenosis and mitral insufficiency. Broadbent is of the opinion that sudden death occurs only in aortic insufficiency, the stenotic lesion is more frequently at fault.<sup>1</sup> Although mild inactive aortic insufficiency is not incompatible with a long active life, it remains a menace because of possible recurrences, progressive valvular deformity and superim-

posed bacterial endocarditis. It is not uncommon for females to develop serious embolic phenomena, especially to the brain. Later in the disease, congestive failure becomes difficult to control and recurs often, with death occurring in a year or two.

## SELECTION OF CASES

Twenty-four † missed cases of "pure" aortic insufficiency due to old rheumatic infections were included in this series. These cases had been overlooked previously on repeated examinations in civilian life as well as in the Army. Although this lesion is frequently associated with other rheumatic valvular lesions, cases of multiple involvement were excluded from this study. No cases were included that were discovered during or immediately following a known attack of rheumatic fever. The aortic diastolic murmur may be entirely absent during the acute attack, then suddenly appear as a faint blow a few days later and become definite in a week, since it may be produced by the slightest retraction or distortion of the valve with resulting slight incompetency. Stenotic lesions require a much longer time to develop.

## ETIOLOGY

Besides rheumatic fever, an aortic diastolic murmur is caused much less frequently by syphilis of the aorta, arteriosclerosis of the aorta and aortic valve, chronic hypertension with dynamic dilatation of the aorta, acute and subacute bacterial endocarditis, rare cases of pernicious anemia or other severe anemias, thyrotoxicosis and congenital aortic-valve defects (bicuspid valve, fenestration). Trauma is a very uncommon cause and is difficult of proof. When functional regurgitation is diagnosed clinically, organic disease is almost always discovered at necropsy.<sup>2</sup> Despite careful studies, the problem of etiology occasionally remains unsolved during life.

**Differentiation from Syphilis.** Untreated syphilis is progressive and eventually the heart and vessels become involved in around half the cases.<sup>3</sup> In untreated cases, symptoms appear after about 15 years with a life expectancy of three more years. In treated cases, the usual period of life expectancy is about five years

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† Since this paper was prepared nine more cases of this type have been recognized.

after the appearance of symptoms. Negative and fluctuating positive serologic tests are not rare in syphilitic cardiovascular disease. Therefore, repeated blood tests are indicated.

In addition to a definite rheumatic history, three of our cases had a history of syphilis within the previous six months. Physical signs of syphilitic aortitis ("tambour" accentuation of second aortic sound, slight widening of the aorta, systolic murmur and transient edema) were never noted. The institution of early antisyphilitic therapy would tend to preclude the development of aortic lesions so soon. Finally, the absence of x-ray widening of the aorta is in favor of rheumatic involvement in these cases.

The following case represents the difficulty encountered when manifestations of syphilis co-exist.

**CASE 1.** A white male, 21 years of age, had an attack of acute rheumatic fever with polyarticular involvement seven years previously. He remained in bed for six months and was informed that he had a heart murmur. He became unable to do any physical exertion because of dyspnea and tachycardia. Six months before induction he contracted a chancre with positive serologic tests. Treatment was begun. A spinal tap was negative. He was inducted ten weeks prior to hospitalization. His symptoms on admission were dyspnea and sharp precordial pains on drilling or marching. He stated that his heart frequently beat rapidly and he tired easily. Appetite had been poor, with a loss of 15 pounds in the past two months.

*Examination* revealed a well-developed but poorly nourished white male in no acute distress. The heart presented an active diffuse apical impulse 8 cm. to the left of the mid-sternal line in the sixth intercostal space. There was a marked sinus arrhythmia with rate of 72 beats per minute. A blowing diastolic murmur was elicited over the second aortic area with transmission down the left sternal border. His blood pressure was 144/66. A Duroziez murmur was present over both femoral arteries. There were several small healed penile scars. The remainder of the examination was negative.

*Laboratory studies* revealed negative serologic tests on three occasions. Urinalysis, blood counts and sedimentation rates were normal. Electrocardiogram, fluoroscopy and teleoroentgenograms were entirely normal. The patient was given a Certificate of Discharge for Disability.

*Discussion.* The problem of rheumatic versus luetic aortic insufficiency is well represented here. However, the evidence appears to favor rheumatic fever as indicated by a definite rheumatic history seven years before with acute polyarthritis, "heart trouble" and subsequent dyspnea and tachycardia on any exertion. The syphilitic infection was of short duration and early antisyphilitic treatment was instituted, followed by three negative blood serologic tests and a negative spinal fluid. There were no symptoms or findings of a previous aortitis, nor was there any widening of the aorta on x-ray and fluoroscopy.

## AGE

Rheumatic involvement of the aortic valve begins most often in childhood<sup>4</sup> and our own case histories bear out this point. The ages in our group of cases ranged from 19 to 42. The average age at the time of discovery of the murmur was 27.2 years. A definite rheumatic history was obtained in 18 of our cases. The average age of initial infection was 13 years, though the range was from 5 to 27 years. There were 21 white males and three negro males. The length of army service at the time of discovery ranged from one week to five years with an average of 12.5 months. Family histories were noncontributory. During this time at least two army examinations were performed. Most of the patients had been under the care of civilian physicians because of definite rheumatic histories.

The majority found military training too arduous and sought medical aid because of symptoms. Six cases were discovered during routine examinations or during treatment for other conditions. Of these, two subsequently gave a definite rheumatic history.

## EARLY SYMPTOMS

There was a remarkable absence of complaints in some cases despite heavy training and duty details. In others, this increased demand upon a seemingly well-functioning heart produced complaints. The order of appearance of early symptoms was: dyspnea (12 times), palpitation or throbbing (11 times), precordial pain (11 times), tachycardia (8 times), swelling of the ankles on prolonged standing (2 times) and dizziness (once). An exercise test should be performed to induce the appearance of latent symptoms. Precordial pain was probably the result of lowered diastolic pressure with a resulting defective coronary circulation. In the active phases of the disease, pain may indicate rheumatic involvement of the pericardium, coronary arteries, or of the aorta with impingement on the coronary ostia. The early appearance of symptoms is frequently dismissed as neurocirculatory asthenia, cardiac neurosis or iatrogenic heart disease.<sup>5</sup>

## THE EARLIEST PHYSICAL FINDINGS

**The Murmur.** If a faint diastolic murmur can be elicited over the aortic areas, the diagnosis of early aortic insufficiency is established.<sup>6</sup> A soft blowing diastolic murmur, usually heard in early diastole, is the first distinctive and most significant finding. It is heard maximally at three areas: (1) at the junction of the sternum and left third costal cartilage (second aortic area); (2) at the junction of the sternum and right second costal cartilage (first aortic area);

and (3) in the fourth intercostal space to the left of the sternum. Early radiation of the murmur is directed downward along the left border of the sternum. Later it may radiate toward the apex, entire precordium or over the back.

If the ventricle is beating strongly and is still able to maintain a high systolic pressure in the aorta, the regurgitant current is more powerful than if the ventricle is beginning to fail and the systolic pressure has dropped to a lower level. The loudness of this murmur does not depend on the extent of the leak but on the velocity of the current from aorta to ventricle. Therefore a faint or decreasing murmur may signify a failing ventricle rather than a small leak.

The murmur was variously described in our series as faint, soft, high-pitched, blowing, streaming and loud or coarse, depending on its intensity and quality. With three exceptions, all the murmurs radiated downward along the left border of the sternum and on two occasions extended to the entire precordium. It was heard best (in all but four instances) over the third left intercostal space or costosternal junction. In only one case was it heard best in the supine position.

#### METHOD OF EXAMINATION FOR MINIMAL LESIONS

Careful comparative studies on the same patients demonstrated conclusively that the murmur probably would not have been missed on previous occasions if examination for aortic regurgitation had followed this procedure: (a) The patient is instructed to hop on each foot alternately 25 times, (b) he then leans forward 45 degrees from the regular sitting position, (c) he is instructed to hold his breath after a forceful expiration, (d) a diaphragm type of stethoscope (Bowles) is applied, and (e) the three areas described above are carefully auscultated (Fig. 1). In rare instances the murmur is heard best horizontally. At the same time, the exercise test tends to reveal early functional difficulties such as dyspnea and tachycardia. A quiet room is essential. Following are two illustrative cases.

**CASE 2.** A white male, 26 years of age, with two weeks of service, injured the left side of his chest while playing football. Because the pain persisted, he went on sick call. Past history revealed diphtheria during childhood but there were no complications. He denied any rheumatic history or cardiorespiratory symptoms.

**Examination** revealed moderate localized tenderness over the ninth and tenth ribs. The heart was not enlarged and presented no murmurs with the ordinary methods of examination. However, following the employment of the procedure previously described, a short high-pitched diastolic

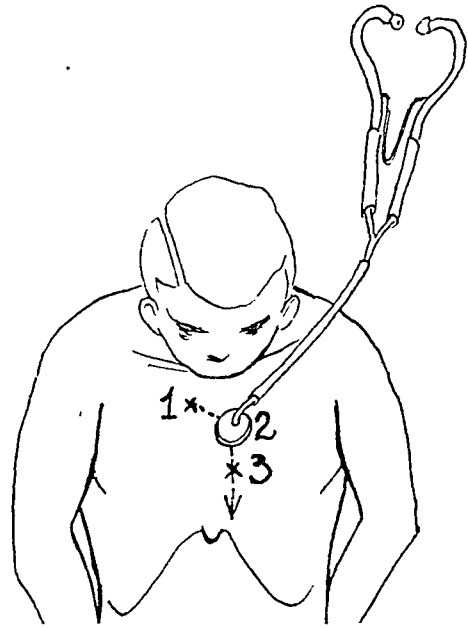


FIG. 1. Examination of the three cardiac areas after exercise, leaning forward during expiration.

murmur was heard over the second aortic area which radiated downward along the left sternal border. The murmur could not be heard with a bell chest piece but was distinctly heard by several observers with the diaphragm (Bowles) attachment. There were no peripheral vascular phenomena. Exercise test revealed no undue cyanosis or dyspnea. Blood pressure was 114/82. Remainder of examination was entirely normal.

**Laboratory studies** included x-rays which revealed fractures of the ninth and tenth ribs near the costochondral junction. Fluoroscopy and x-rays of the heart and electrocardiogram were normal. A small symptomless diverticulum of the esophagus was noted at the level of the fifth dorsal vertebra. Kahn, urinalysis, sedimentation rate, blood counts were all normal. The vital capacity was 3,400 cc.

**Course.** The chest pain decreased with the healing of the ribs. Because the minimal lesion produced no further functional impairment as evidenced by exercise tests and absent symptomatology, he was put on limited duty.

**CASE 3.** A white male, 35 years of age, with five months service developed pain in the left axillary line at the sixth interspace during the last two months of his basic training. It was brought on by exercise but he could obtain relief with a 15 or 20 minute rest period. He was able to march up to two and a half miles before the pain would appear but continued marching did not cause it to become unbearable. However, the continued exercise produced epigastric distress and a "light-headed feeling."

**Examination** revealed a well-developed, well-nourished male in no distress. The heart was entirely negative except for the presence of a short high-pitched diastolic murmur heard over all three aortic areas and transmitted downward along the left sternal border. This was heard only after the patient was examined in the recommended manner. The murmur was not elicited after ordinary examina-

tion in a comparative study. The exercise test precipitated precordial pain.

*Laboratory Studies.* X-ray and fluoroscopy were normal. Serial electrocardiograms were normal. Urinalysis and blood counts were negative.

*Course.* Because the patient did very well in a Reconditioning Unit, he was given a trial at duty. However, he had a recurrence of his symptoms and was finally discharged from the service.

## SECOND AORTIC SOUND

To avoid confusion with the murmur or the pulmonary sounds, auscultation of the second aortic sound is best performed over the neck vessels. If absent or diminished it indicates that the valves are so defective as to be unable to produce the necessary check. In our series, the second aortic sound was considered abnormal only twice. On one occasion it was described as completely absent and once as "tambour-like."

## LEFT VENTRICULAR ENLARGEMENT

Very slight degrees of enlargement were described four times but x-rays failed to corroborate it on one occasion. In two other cases, fluoroscopy and x-ray uncovered slight enlargement which was not found on physical examination. With minimal aortic valve involvement, enlargement of the heart is an unusual finding. A diastolic thrill over the aortic area was not encountered because of the slight involvement and is usually absent even in advanced disease. An Austin Flint murmur was elicited on two occasions, and in both instances, the aortic diastolic murmur was described as loud and blowing. One of these cases had the widest pulse pressure of the series but cardiac enlargement and axis deviation were not noted. The highest systolic pressure recorded was 180 mm. of mercury and the lowest diastolic pressure was "zero." The average systolic was 140 while the average diastolic was 68. The average pulse pressure for the series was 72 mm. of mercury. Careful recording of Korotkow's fourth and fifth sounds is important if blood pressure readings are to be of diagnostic value.

## PERIPHERAL VASCULAR SIGNS

Unless there is considerable reflux, peripheral vascular signs may not be present. Their appearance has been interpreted as due to reflux into the left ventricle with decreased tension in the arterial tree; or, due to reflux of the blood from the peripheral arteries into the aorta.

In order of frequency and importance, peripheral vascular signs usually occur as follows: Corrigan pulse, increased pulse pressure, capillary pulse, double femoral murmur (Duroziez), visible arterial pulsations, delayed arterial pulse, femoral pistol-shot sound, and

Traube's femoral tones. In our series of cases with minimal involvement, Duroziez murmur was heard nine times and capillary pulsations, femoral pistol-shot sound and Corrigan pulse, twice each. The optic fundus should also be searched for capillary pulsations. Capillary pulsations at the finger-nail beds are also characteristic. It is unnecessary to wait for the appearance of any of these signs which already indicate increasing pulse pressure. The elicitation of the diastolic murmur as previously described is adequate to establish the diagnosis of aortic insufficiency. If corroborative peripheral vascular signs are awaited to make the diagnosis, more than half of the early cases will be missed.

## ELECTROCARDIOGRAMS

Sinus tachycardia was noted twice. Left-axis deviation and tendency to left-axis deviation were recorded twice each. There was no uniform correlation with cardiac enlargement. Two cases revealed evidences of myocardial damage. All other laboratory studies were noncontributory. All sedimentation rates and white blood counts with differential counts were normal on admission to help rule out any active inflammatory lesions. The question of serologic tests has been considered.

## CONCLUSIONS

1. A re-evaluation of 24 cases of minimal "pure" rheumatic aortic insufficiency that had been repeatedly missed is presented. A method of physical diagnosis which has been useful in the earlier detection of this lesion is described and recommended.

2. The faintest diastolic murmur which can be elicited over the aortic areas establishes most often the presence of an organic lesion, even before corroborative signs make their appearance. Earlier diagnosis and treatment in the incipient stages (whether the lesion is rheumatic or syphilitic in origin) may prevent more serious phases of heart disease later.

## BIBLIOGRAPHY

1. Reich, N. E.: Calcific aortic valve stenosis: a clinicopathologic correlation of 22 cases, *Ann. Int. Med.*, 22:244-252, 1945.
2. White, P. D.: *Heart Disease*, ed. 2, New York, Macmillan, 1938, p. 452.
3. Stokes, J. H., H. Beerman, and N. R. Ingraham: *Modern Clinical Syphilology*, ed. 3, Philadelphia, Saunders, 1944, p. 893.
4. Tice, F.: *Practice of Medicine*, Hagerstown, Md., Prior, 6:293, 1945.
5. Auerback, A., and P. A. Gliebe: Iatrogenic heart disease, *J. A. M. A.*, 129:338 (Sept. 29) 1945.
6. Reich, N. E.: Protean manifestations of acute rheumatic fever. To appear shortly.

## Operations to Produce Sterility: Medicolegal Implications

### Medical Aspects

FREDERICK H. FALLS,<sup>†</sup> M.D.

When I was asked to assume the duty of handling the medical aspect of this subject, I felt that there were two main objectives that should be set forth: First, to present to all of you the problems of sterilization which come before doctors and need solution in the interests of the mother, the family and society. Second, I thought it would be of value to acquaint the legal members of this group with the fundamental anatomy and physiology of fertility, so that they may be able better to comprehend what a doctor does when he performs a sterilizing operation, and why these operations are not always done in the same way.

In considering the medical indications for therapeutic sterilization, it must be understood that the facts upon which such a recommendation rests are not too fixed or determined. The physician must determine as a rule, not only the danger that is present for the patient at the time he is asked to consider sterilization, and what the probable effects will be if repeated pregnancies are allowed to occur, but also what effect the operation will have on the future happiness of the mother, her husband and other children in the family if sterilization is performed.

These problems which confront the physician in the daily practice of medicine are not always simple. The proper solution varies widely in different cases depending upon attending circumstances of medical, social, ethical and religious significance.

As a rule the objective in the doctor's mind is the protection of the individual, her family and society as a whole from dangers which in his opinion will occur if the individual is allowed to become pregnant and bear a child.

Any operative procedure which will prevent the union of spermatozoa and ovum, or stop the embedding and development of the fertilized ovum in the uterus can be termed a sterilizing operation. Although other methods have been tried and suggested, the operative method of sterilization is in general the

most successful and the most widely practiced. While it is true that various operative procedures to be described all give good results in most cases, there is no procedure that is infallible except the complete removal of the sex glands in either the male or female.

In order to present the anatomic facts for your consideration, I wish to show some drawings which I have had prepared for teaching purposes at the University of Illinois College of Medicine.

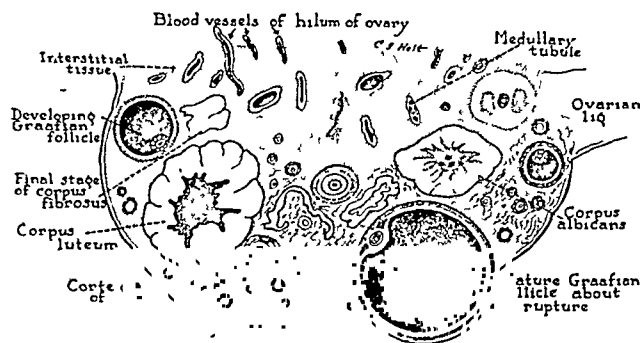


FIG. 1. Cross-section of the human ovary.

Figure 1 is a cross-section of the human ovary. It is diagrammatic in the sense that there are various bodies present which do not all occur in the ovary at the same time, but we prepared it to show a human ovum in what is called the graafian follicle, immediately preceding the rupture which sets the ovum free and extrudes it into the abdominal cavity. Also shown are immature follicles ready to develop. Each month one develops and one ovum is set free and extruded into the abdominal cavity. Later on we will discuss the effect on the ovum of the x-ray treatment to produce sterilization. The way this agent produces sterilization is to inhibit the development from the resting stage of the follicle to the completion of the follicle, with the extrusion of the ovum. I will have more to say about that later.

Figure 2 shows the anatomy of the uterus, the tubes and the ovaries. One quadrant of the uterus has been cut away to reveal the connection between the vagina, the uterine cavity, the tube and the abdominal

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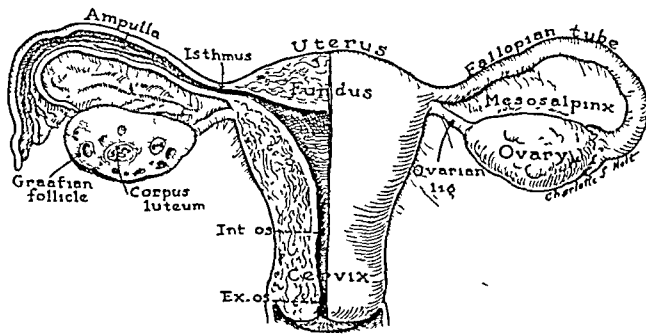


FIG. 2. Anatomy of the uterus, the tubes and the ovaries

cavity. The proximity of the tube and the ovary, is illustrated in this drawing.

By damaging the endometrium, or lining membrane of the uterus, sterility may be produced. Damaging the fallopian tube, by crushing it or tying it off, may produce sterility. Sterility, of course, can be produced by taking out the uterus, or by taking out both ovaries. As far as the female is concerned, those are the principal factors upon which fertility depends.

Figure 3 illustrates the pathway of the spermatozoa deposited in the vagina, ascending into the tube, and the place of union when fertilization takes place in the tube. The fertilized ovum is then transported down into the uterus, embeds itself in the lining of the uterine cavity, and in that position the fetus develops under normal circumstances. We will speak later on ectopic pregnancy where, in the most common form, the ovum has been fertilized in the tube and attempts to get it down into the uterus to embed, are unsuccessful. The result is a tubal form of ectopic pregnancy. The union of the ovum and the spermatozoon is shown at the top of Figure 3. Only one spermatozoon can get through the capsule of the ovum, and its size, as compared with the ovum, is indicated. That union produces fertilization. Then the fertilized egg comes

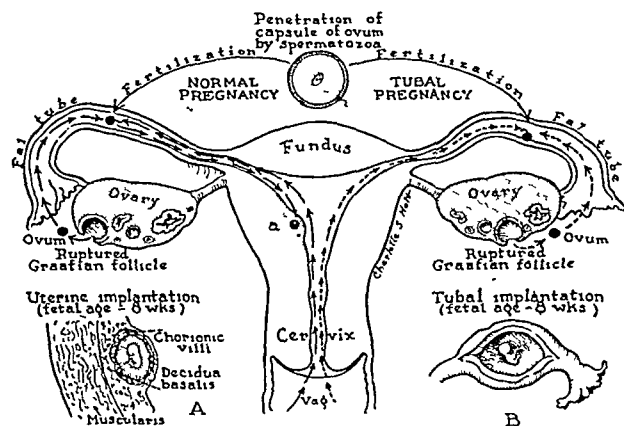


FIG. 3. Path of sperm, fertilization, and implantation, (A) uterine, (B) tubal.

down the tube into the uterus and you see in A the beginning development of the fetus in the lining membrane of the uterus.

Figure 4 illustrates a uterus upon which a caesarean section has been done. The uterus has been repaired after removal of the baby and it seems best that the woman be not allowed to become pregnant again. The uterus is turned to one side, and the tube is picked up and a portion taken out of the tube. A little portion is cut out of the uterus and then the uterine wall is sewn together. The tube is shown going through the uterine wall. This is sewn together so as to exclude this portion of the tube from the peritoneal cavity. That is one of the standard, and probably the most successful types of operation for sterilization. A sterilizing operation can be done

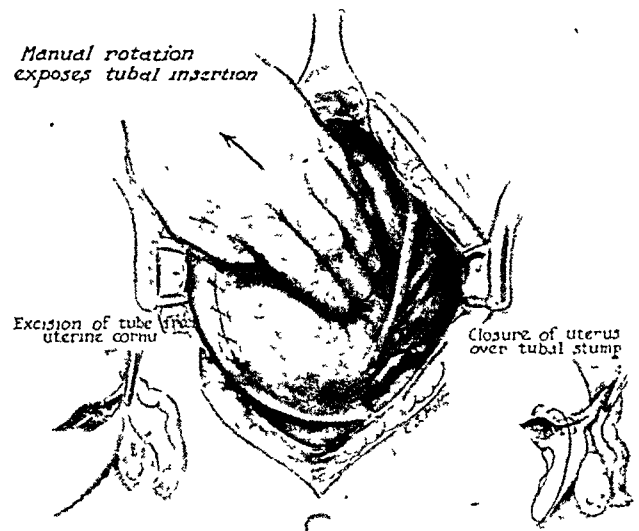


FIG. 4. Tubal sterilization.

without doing a caesarean section, immediately following childbirth or within a day or two. It is possible to make a small incision in the abdominal wall, even under local anesthesia, and rotate the enlarged uterus in such a way that the tube comes into view and then a portion of the tube can be excised.

Figure 5 illustrates a similar type of operation. This operation is done on an immature fetus because in this particular case a serious toxemia threatened the life of the mother. The pregnancy is interrupted and because the condition is one that will progress in spite of the termination of this pregnancy and other treatment, sterilization is carried out at the same time.

Figure 6 illustrates the possibility of performing this operation of sterilization vaginally. The cervix of the uterus can be pulled down, the abdominal cavity can be opened between the uterus and the bladder, the uterus can then be turned over and the tube will

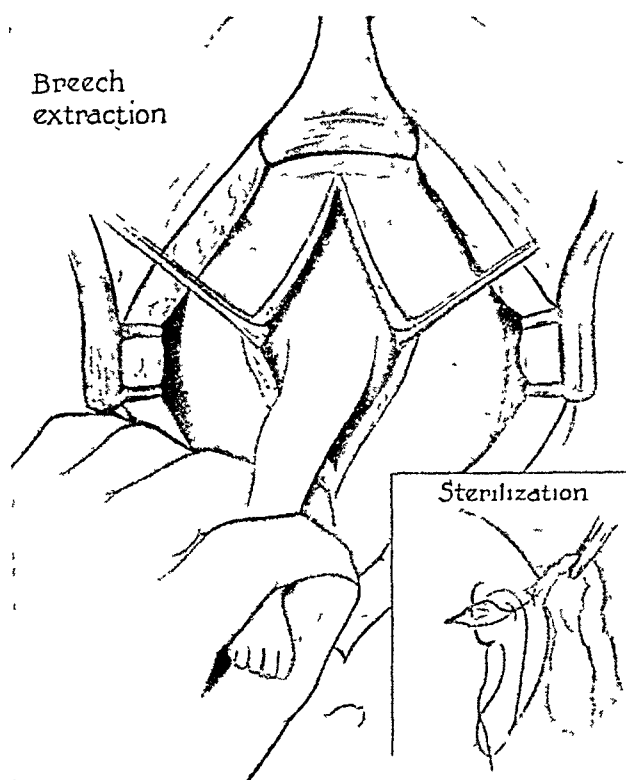


FIG. 5. Abdominal hysterotomy (fifth month).

be found in this position. We show an ectopic pregnancy here, which has nothing to do with the discussion that we have before us; but the possibility of doing a sterilizing operation without making an abdominal incision should be understood by the members of the legal profession.

It will be seen that the ovum develops in the ovary (in the graafian follicle) and that about the 14th day after the beginning of the menstrual period it is extruded and picked up by the fallopian tube and transported downward toward the uterus. In the tube it is met by numerous spermatozoa which have been deposited in the vagina and by their own motility have worked their way up through the cervix of the uterus and the uterine canal into the tubes. In order, therefore, to produce sterility in a given individual it is necessary to prevent the production of the germinal cells or to produce an efficient barrier to their union, or to render the generative tract of the mother unfavorable for the development of these cells into a mature baby.

#### METHODS FOR PRODUCING STERILIZATION

There are various ways of accomplishing these results, some of which seem to be particularly applicable to certain types of cases. Probably the one most commonly used is the surgical method. In this

method the abdomen is opened as for any abdominal operation, the tube is brought up and a small segment including a portion of the tube which penetrates the uterine wall is excised and the defect in the broad ligament and in the horn of the uterus is closed. This is a very efficient method, although failures have been recorded. A corollary of this method has been recommended for temporary sterilization. In this method the outer end of the fallopian tube is buried between the leaves of the broad ligament—that is the ligament just below these tubes that I showed you on the drawings—and sutured in this position. If the need for sterilization is removed the tubes can be withdrawn from the broad ligament and will still function. This method is not so reliable either as an efficient method of sterilization nor does it insure fertility after freeing the tube, and is not often recommended.

The Madlener technic depends on crushing the tube with an artery forceps and tying the crushed tube in addition with silk (unabsorbable) ligatures. It would seem that this method would be quite efficient, but many failures have been reported, about one per cent in some series.

Removal of the ovaries will of course result in total permanent sterilization, if there is no accessory ovarian tissue. Removal of the body of the uterus should accomplish the same result, but pregnancy in the cervical stump has occurred in some cases. Removal of both fallopian tubes almost always sterilizes

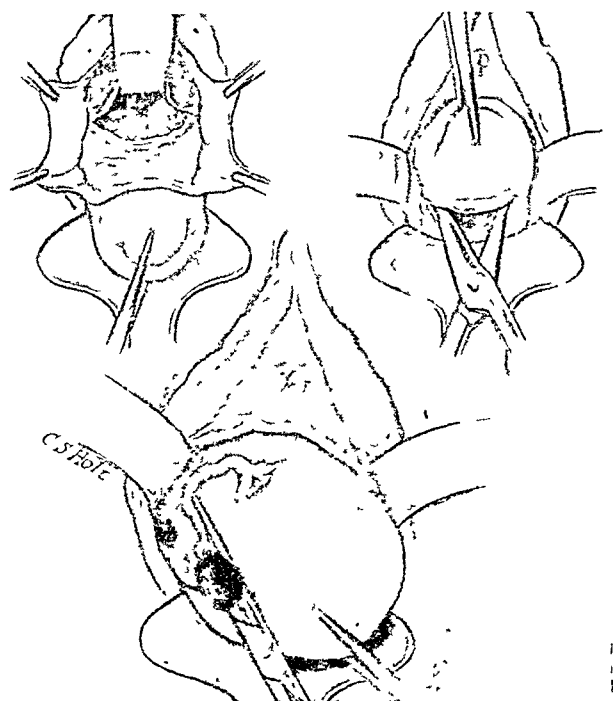


FIG. 6. Removal of ectopic by colpotomy.



the patient, especially if a small piece is taken out of the uterine wall at the point where the tube penetrates it.

**Puerperal Sterilization.** Relatively recently there has been proposed a method of sterilization to be done immediately after the birth of a baby in cases where future pregnancies should be prohibited. After childbirth the uterus is so large that it remains as an abdominal organ for about ten days. During this time it is a simple procedure to make a small opening in the midline of the abdominal wall under local anesthesia, rotate the uterus on its long axis until one tube can be brought up to the opening and the sterilizing procedure carried out. The uterus is then rotated again until the opposite tube can be treated in the same way. Several series of 100 or more cases have been reported with good results and no mortality.

**Vaginal Sterilization.** The operation may be done vaginally in most cases if there are serious contraindications to opening the abdomen from above. In this approach the vaginal wall is incised, the uterus and bladder are separated, the peritoneal cavity is opened, the body of the uterus tipped forward, which renders the uterine end of the fallopian tubes, together with a small portion of the tube running into the horn of the uterus, easily accessible for removal.

Another method not so popular has been the use of an electric cautery introduced through the cervix of the uterus after dilation of the latter, and cauterization of the end of the tube as it enters the uterine cavity. The healing of the resultant burn causes contraction and closes off the tube. This can be done without any cutting operation.

**Radium and X-ray Sterilization.** Sterilization may be effected by the use of roentgen rays. In this method the rays are directed at the ovaries. At birth a girl baby is estimated to have about 30,000 ova in each ovary. These lie dormant until the age of puberty at which time one ovum becomes mature each month in a graafian follicle. The follicle ruptures, setting free the ovum for fertilization. These ova, because of their highly specialized nature, are highly vulnerable to the action of roentgen rays.

Sufficient exposure is used to cause an inhibition of development of graafian follicles in the ovary, and hence no ova are extruded. If the dosage is not too large the sterilization may be temporary instead of permanent, and after several months follicles form in the ovaries again and the menstrual cycle is resumed. When large doses are used to produce permanent sterilization, the destruction of all ovarian function forms an undesirable feature of this type of sterilization. The same objection holds good for the x-ray treatment of the male gonads to produce sterility. If you

produce sterility by means of x-ray, you also destroy the internal secretions of the ovaries or the testicles.

Radium may also be used to produce sterilization. Its action, however, is based on a different principle. The radium rays have less ability to penetrate deeply, and so they do not affect the ovaries primarily, but act chiefly on the lining membrane of the uterus, causing changes to occur which render it unfavorable for the embedding of a fertilized ovum. This method is not certain unless a rather large dose is given and is rarely used except incidental to the treatment of such gynecologic pathology as benign or malignant tumors of the uterus.

More recently a method has been reported by Power and Baines by which, under local anesthesia, a peritoneoscope—that is a tube which has an electric light in it—is introduced through the abdominal wall. Air is introduced into the abdominal cavity. The tubes are grasped near the uterus, and an electric current cauterizes them for a distance of one centimeter. The patient is allowed to leave the hospital in 12 to 18 hours. They have not reported the number of cases in which this procedure has been carried out, or what the results have been.

**Other Methods of Sterilization.** In the male, vasectomy or interruption of the pathway by which the spermatozoa travel from the testicle to the ejaculatory ducts is a relatively simple procedure which can be done under local anesthesia and without entering the abdominal cavity. It has no ill-effects on the production of testicular hormones and it preserves the possibility of fertility being re-established by operative correction of the condition, if this becomes desirable at a later date. The removal of the testicles by castration is an absolute method, but is open to the objection of removing all testicular hormones.

Attempts have been made to produce antibodies in the blood of female animals antagonistic to the spermatozoa—spermattoxins, they are called—for the purpose of destroying these cells in the generative tract before or immediately after fertilization occurs, thus producing sterility. A measure of success has been attained in animal experiments, but the method has not been successfully applied to human sterilization problems as far as I have been able to ascertain.

## INDICATIONS FOR STERILIZATION

The physician is continually being faced with the necessity of considering sterilizing operations on his patients by the medical conditions which he finds upon examination during the prenatal period, or during or just after labor, and during and preceding gynecologic operations.

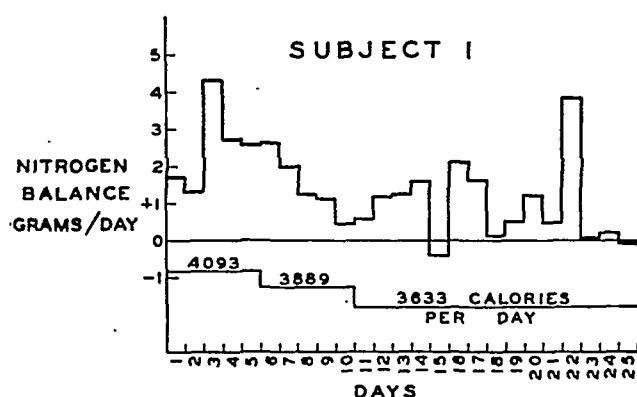


FIG. 1. A nitrogen balance study of a normal adult human for 25 consecutive days using partially hydrolyzed lactalbumin as the sole source of nitrogen.

The net nitrogen balances for the three subjects are shown in graphic form in Figures 1, 2, and 3. For subjects 1, 2 and 3 the average daily retention was 1.43 Gm., 1.50 Gm., and 2.04 Gm., respectively, on a nitrogen intake of 194 mg., 175 mg., and 223 mg. per kilogram of body weight. Upon reduction of the caloric intake of subjects 1 and 2, there was a decrease in the average daily nitrogen retention; the nitrogen intake remained the same. When the caloric intake of subject 1 was reduced from 50 to 47.5 Cal./kilo, the average retention of nitrogen dropped from 2.74 Gm. to 1.51 Gm. per day; a further reduction to 44.4 Cal./kilo was followed by a fall in the average retention to 0.97 Gm. of nitrogen per day. Comparable reductions in the caloric intake of subject 2 were followed by a fall in the average daily retention of nitrogen from 2.72 to 2.27 Gm. and finally to 0.88 Gm. The caloric and nitrogen intake of subject 3 was kept constant.

In our previous study<sup>12</sup> using Parenamine, acid hydrolyzed casein fortified with one per cent dl-tryptophane, it was reported that approximately 50 Cal./kilo were necessary for the maintenance of a positive nitrogen balance with a nitrogen intake of about 200 mg. per kilogram of body weight. Therefore, the same number of calories and approximately the same level of nitrogen intake were used initially in this study. A marked positive balance was observed and since the two male subjects did not want to gain weight their caloric intake was reduced but the nitrogen kept constant. It was interesting to observe the decrease in the amount of nitrogen retained by these two subjects upon reduction of their daily caloric intake. In our previous report<sup>12</sup> the same relationship of total calories to nitrogen retention was observed; i.e., an increase in the number of calories resulted in an increased nitrogen retention.

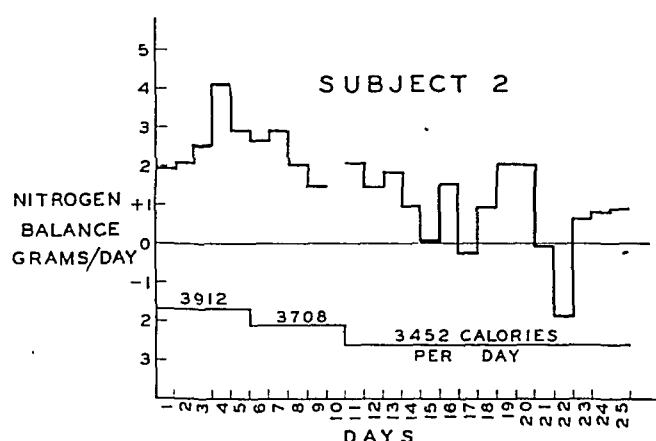


FIG. 2. A nitrogen balance study of a normal adult human for 25 consecutive days using partially hydrolyzed lactalbumin as the sole source of nitrogen.

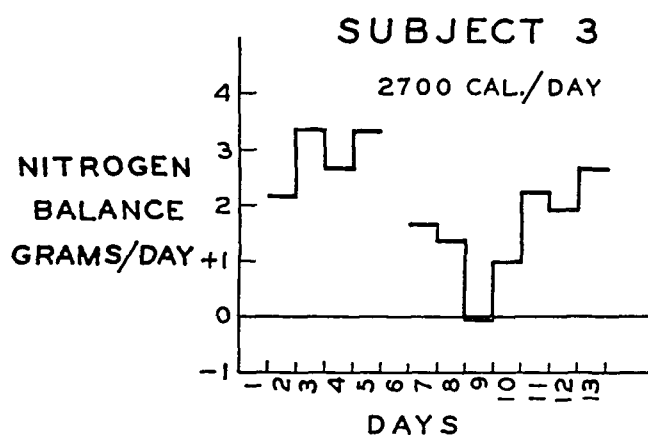


FIG. 3. A nitrogen balance study of a normal adult human for 13 consecutive days using partially hydrolyzed lactalbumin as the sole source of nitrogen.

On diets in which nitrogen was provided by amino acids from Parenamine a total caloric intake of 50 Cal./kilo was required before a positive balance was observed in two normal adults when the nitrogen intake was about 200 mg. per kilogram of body weight. The average daily retention was 0.61 Gm. and 0.68 Gm. of nitrogen on diets containing 191 mg. and 211 mg. of nitrogen per kilogram of body weight, respectively. When the nitrogen was provided by Essenamine only 44 Cal./kilo were required, and the average daily nitrogen retained was 0.88 Gm. and 0.97 Gm. with diets containing 175 mg. and 194 mg. of nitrogen per kilogram of body weight, respectively. These data indicated that the total caloric requirement with the use of partially hydrolyzed lactalbumin as the sole source of nitrogen is less than with acid hydrolyzed casein fortified with one per cent dl-tryptophane. This may be due to the relative amount of essential amino acids provided by lactalbu-

min as compared to acid hydrolyzed casein fortified with one per cent dl-tryptophane.

### SUMMARY

1. It was demonstrated that partially hydrolyzed lactalbumin (Essenamine) is an adequate source of nitrogen for the maintenance of nitrogen equilibrium.

2. Two adult men and one woman were maintained in positive nitrogen balance on a synthetic diet in which Essenamine was the sole source of nitrogen for 13 to 25 days. The average daily retention of nitrogen was 1.43, 1.50, and 2.04 Gm. per day on intakes of 194 mg., 175 mg., and 223 mg. of nitrogen per kilo of body weight, respectively.

3. No attempt was made to maintain a basal level of either nitrogen or calories. Variations in the caloric intake on a fixed level of dietary nitrogen affect the daily nitrogen retention. A decrease in calories caused a large drop in amount of nitrogen retained.

### BIBLIOGRAPHY

1. Rose, W. C.: The role of protein in the diet, *Proc. Inst. Med. Chicago*, (June) 1944.
2. Shohl, A. T., A. M. Butler, K. D. Blackfan, and E. Mac-

Lachlan: Nitrogen metabolism during the oral and parenteral administration of the amino acids of hydrolyzed casein, *J. A. M. A.*, 15:469, 1939.

3. Altshuler, S. S., M. Sahyun, H. Schneider, and D. Satriano: Clinical use of amino acids for the maintenance of nitrogen equilibrium, *J. A. M. A.*, 121:163, 1943.
4. Elman, R., and D. O. Weiner: Intravenous alimentation, *J. A. M. A.*, 112:796, 1939.
5. Kade, C. F.: Unpublished data.
6. Ma, T. S., and G. Zuazage: Micro-Kjeldahl determination of nitrogen, *Ind. & Eng. Chem., Anal. Ed.*, 14: 280, 1942.
7. Folin, O.: On the determination of creatinine and creatine in urine, *J. Biol. Chem.*, 17:469, 1914.
8. Peters, J. H.: The determination of creatinine and creatine in blood and urine with the photoelectric colorimeter, *J. Biol. Chem.*, 146:179, 1942.
9. Albanese, A. A., and V. Irby: Determination of urinary amino nitrogen by the copper method, *J. Biol. Chem.*, 153:583, 1944.
10. Peters, J. P., and D. D. Van Slyke: *Quantitative Clinical Chemistry*, vol. II, Baltimore, Williams & Wilkins, 1932, p. 77.
11. Jones, J. H., and C. Foster: A salt mixture for use with basal diets either low or high in phosphorus, *J. Nutrition*, 24:245, 1942.
12. Soenke, M. L., M. G. Horning, and E. H. Watson: Maintaining nitrogen balance with amino acids. *Am. Pract.*, 1:276, 1947.

## BOOK REVIEW . . .

THE SECOND FORTY YEARS. By Edward J. Stieglitz, M.D. 317 pages. Philadelphia, Lippincott, 1946. Price \$2.95.

The reviewer of this book usually views with a jaundiced eye the "medical" book written for the layman. In this instance, however, he is most enthusiastic. If the intelligent layman becomes as absorbed in reading this volume as the reviewer has, he will find it most instructive and interesting. The author has presented the medical information in a fashion that is simple, direct and understandable to the intelligent nonmedical reader but at no time does he insult the reader's intelligence by "talking down" to him.

Everyone reaching middle life cannot help but think of the oncoming years and what they may bring in health, or disease. Will these years provide vitality and endurance to carry on in the person's activities or must he anticipate a "running down" as of a clock! This volume will help greatly in dispelling the fears and anxieties which accompany the anticipation of

the second forty years. It will dissipate the old wives' tales and superstitions which are handed from generation to generation concerning physiologic changes which occur with aging.

The author first discusses the biology of senescence. Then he considers certain of the diseases of aging—hypertension, heart disease, cancer and nutritive disturbances. The changes in the sexual sphere with passing years are presented in a most rational manner. Finally there are several philosophical chapters on the problem of aging.

The choice of this book by the American Association for the Advancement of Science as one of its Non-technical Science Series books is a testimonial of its high caliber. The reviewer must urge the physician to recommend this volume to his intelligent middle-aged patient who wishes to know what future years hold in store for him, and especially to that patient who is beset by doubts and fears.

R. H. K.

# Cases from the Medical Grand Rounds Massachusetts General Hospital

Edited by LEWIS K. DAHL, M.D.

BOSTON, MASSACHUSETTS

## CASE 13

### LEAD POISONING

DR. WALTER BAUER: The patient we are presenting is suffering from an industrial disease, which, when I first arrived here in 1928 was seen with great regularity, due to the presence of Dr. Joseph C. Aub and his interest in plumbism. This patient is being shown because he illustrates a number of things, one of these being the hazard to the worker in a certain type of industry, even where industrial hygiene is evidently very well supervised.

He presented, when he arrived in the Emergency Ward, the usual diagnostic problems. In fact, we have some reason to believe that the operation which was performed some weeks prior to his entry here, may be explained on the basis of his lead colic. And then I thought it would be very worthwhile to review the immediate treatment of lead colic as well as subsequent treatment of a patient of this type. Dr. Mellinger will present the case.

DR. GEORGE W. MELLINGER: This is Mr. B., No. 560019, who is 24 years old. His story began about two and one-half months ago, when, following eight or nine hours of anorexia, he began to have rather severe lower abdominal pain. This was rather colicky in nature and would migrate from side to side, not staying in any one place very long. The attacks of pain would last from about one to two hours and then go away and return again one or two hours later. He had four, five, or six attacks per day. At the same time he became constipated and began to vomit most of his food. After four days he went to his doctor who referred him into another hospital where they studied him for two or three days, and following a three-hour period of constant pain in the right lower quadrant, it was decided to operate and remove his appendix. That was done and for one month after operation the patient had no complaints at all. Then, one and one-half months ago he began to have similar pains in the same distribution, but this time less severe. This time they lasted only about four days and went away again. The present attack of pain began about three days before admission. At that time he

began to have fairly mild abdominal pain, but two days before admission very severe pain, the most severe which he had ever had. It was almost constant, with severe colicky episodes at intervals of several hours. The pain again was located in the lower abdomen, mostly on the left, but somewhat on the right; it would again migrate from side to side. At the same time he became constipated and vomited everything which he ate.

The occupational history of this man reveals that he has worked for the past six months in a plant manufacturing lead storage batteries. His job has been on the assembly line and varies from time to time. Sometimes he does what is called "burning," which consists of welding the lead plates; sometimes he inserts the wooden separators, and sometimes other jobs, but always on the assembly line. This plant is well aware of the nature of lead poisoning and has taken various precautions, such as ventilation, the use of masks and rubber coated cotton gloves. Industrial studies of this plant reveal that there is a sufficient concentration of lead in the air where the patient works to explain his symptoms. Examinations of the urine of fellow workers who work in the same vicinity reveal that they have urinary lead excretions of sufficient degree to indicate that there is danger of lead poisoning in the plant.

Physical examination on admission on January 18, 1947 revealed a well-developed, well-nourished male, in very acute abdominal pain. He was also somewhat dehydrated. The parotid glands showed some enlargement. There was a marked lead line around the teeth, especially around several carious teeth. A fresh appendectomy scar was present on the abdomen. Considerable spasm of the abdominal wall was found but peristalsis was normal even during the severe episodes of colic. Otherwise the physical examination was within normal limits.

Urine examination on admission was completely normal with the exception of a "green-without-sugar" test and many coarsely granular and finely granular casts. White blood cell count was 13,000; red blood cell count 4,620,000 and the hemoglobin 12.5 Gm. A differential count showed a slight shift to the left.

The red cells showed many cells with basophilic stippling and many more showed polychromatophilia.

X-rays taken in the Emergency Ward at the time of admission showed the transverse colon to be markedly dilated but a barium enema revealed no evidence of obstruction.

Treatment for the acute colic in the Emergency Ward consisted of the following drugs: calcium levulinate 1 Gm. given intravenously, without immediate relief, followed by a constant intravenous drip of normal saline containing 2 Gm. of calcium levulinate. This gave moderate but not complete relief for one or two hours. Demerol, 100 mg. subcutaneously, gave complete relief for one and one-half hours. Subsequently he got the same relief with Demerol for three, four, or five hours. Atropine gave no relief from the pain. Tetraethylammonium chloride, which is a sympathetic-paralyzing drug, produced complete relief of the pain for 45 minutes in the Emergency Ward. He has not been given that since. Since the patient came to the ward, treatment has consisted of calcium chloride intravenously. That was given because it is more concentrated in calcium than the levulinate. It has to be given much more slowly, however. He was given a high calcium diet, lots of milk and cheese, and also 8 Gm. of sodium citrate daily.

Blood chemistry tests were all within normal limits, with the exception of the nonprotein nitrogen which was 57 on admission but two days later was normal. His  $\text{CO}_2$  was slightly elevated, 31.8 m.eq./l. Chloride, calcium, and phosphorus were within normal limits. The lead excretion done by the Occupational Hygiene Division at the State House revealed an excretion of 0.33 and 0.31 mg. of lead per liter, with normal excretion being 0.08 mg. per liter. This is sufficient concentration to explain his symptoms. In acute lead poisoning excretion may reach 0.5 mg. per liter.

The first and second day he had almost constant pain and had relief only when he got Demerol or other medication. On the third day he had about three or four acute episodes of pain relieved by Demerol. On the fourth day he had two rather severe episodes of pain but much milder than the one he had when he came in. On the fifth day he had just one very mild episode of pain along in the evening. During the last eight days he has had no pain at all, is feeling fine and eating well.

DR. BAUER: The patient has never had any evidence of neurologic abnormality. As Dr. Mellinger states, he is symptom-free and has been for a period of a week. He does have a very obvious lead line.

It seems to me when you go back over it that I

would have expected he could have been brought under complete control as regards pain more rapidly than was done in this instance. When in the Emergency Ward, having pain in the belly; he was the property of the Surgical Service, and they insisted that the man be examined in great detail and have a barium enema, which I am sure did not help the patient, particularly if he did not expel all of it soon thereafter. In retrospect, one wishes that, even during the period that they were observing this man to be certain that he did not have an intestinal obstruction, he had had the benefit of treatment for acute plumbism which would have done him no harm: An enema to be certain his large bowel was empty; or an atropinization, and really see that it was complete; and the calcium chloride intravenously in larger amounts than were given. As I remember patients that we saw in the past, once we were sure we were dealing with no acute abdominal condition, we always administered Epsom salts. On that program these people were usually brought under control, completely free of pain, within a period of 24 to 48 hours. I have been rather opposed to deleading this individual, because of having seen several patients in this hospital who as soon as they became symptom-free, or within a few days thereafter, were put on an active deleading regime only to have an encephalitis occur in two instances, one with an associated optic atrophy.

This man is going to quit his job, and I would be inclined to let him seek some other type of work, stay on a high calcium regime and forego the privilege of deleading him, feeling that he will continue to excrete small amounts of lead for a long period of time. I think Dr. Aub probably feels, or I am informed that he feels, that it would probably be wiser or would be worthwhile to delead him at this time, feeling, very likely, that more lead could be mobilized and that he would have a minimum amount of lead left in his skeletal system. Dr. Aub, would you care to make further remarks?

DR. JOSEPH C. AUB: I suppose there are two questions you would like me to answer. One is the acute treatment of this patient and the second one is the one Dr. Bauer teased me with, whether one should delead this man. Let us take up the first question. Why did calcium gluconate or levulinate appear to be not effective in this man? What is the explanation of lead colic? He was having pain because the muscles of the intestines were in a state of increased tonicity. In certain areas in the intestines this tonicity became so great that the lumen was practically closed, essentially a temporary obstruction, and then a peristaltic

wave approached, and produced increased pressure above the obstruction and the patient felt pain. The pain oscillated from one place to another because areas of temporary obstruction appeared and disappeared in different areas.

Many years ago by taking smooth muscle strips which had no nerve cells at all in them and by exposing them to lead we observed increased tonicity. So we thought that lead worked by direct action on the smooth muscle without needing the influence of the sympathetic system. Of course, the fact that tetraethylammonium worked well implies that the sympathetic nervous system may well play a part in colic. I think more work ought to be done on that problem.

Calcium chloride, in spite of not being very effective in this patient, usually works extraordinarily well. That is hard for me to say, because we first recommended it, but I have never seen any medication that works better. Do you agree with that, Dr. Bauer?

DR. BAUER: I always thought that it worked dramatically.

DR. AUB: I think the reason it did not work on this man was because he had a very severe lead colic. Tanquerel des Planches said, more than 100 years ago, that lead colic remained severe for 12 days after the patients came into the hospital if they were given no medication. If this patient had been given calcium chloride or one of the other calcium salts more frequently, I am convinced that his lead colic would have stopped more readily. I also assume that the fact that Demerol worked was due to a summation of inadequate stimuli, because the more medication given, the more readily is the colic stopped. He would have responded also if he had been given more calcium salts.

Now, as to whether this man should be given deleading. He has been exposed to lead heavily and recently, and lead will be present in high concentration in his bone trabeculae. The bone trabeculae will have 11 to 12 or 15 times as much lead per gram of calcium as will be present in the cortex. If a person is exposed to small quantities of lead over many years, that is not so, but a person who is recently exposed to lead (or any heavy metal with an insoluble phosphate) has much more of this metal in the trabeculae than in the cortex. That lead is liberated at a quite rapid rate, circulates and gets excreted or re-deposited, and more and more of it gets into the cortex. This is the only type of patient who deserves deleading, I think, now. I think a person who is exposed to small quantities of lead over the years does not deserve deleading, because his lead is more evenly

distributed throughout the bones and cannot be liberated well. A fair amount of lead in this case might be liberated, because it is in an area of the bone which is easily mobilized, the bone trabeculae.

Is it worth doing? People who are interested in lead poisoning disagree. Some agree with what Dr. Bauer just stated: Let him get rid of it gradually himself. Others think the patient gets back to work and feels well more rapidly if deleading is done under careful supervision. I think they feel well faster and that disability is materially shortened, but I am not nearly as enthusiastic about vigorous deleading as I used to be, because I think, if left alone, the patients get well by gradually eliminating a good percentage of their lead.

The fact that a low calcium diet and ammonium chloride may produce a recurrence of colic shows that it does liberate lead. Therapeutic deleading can be done gradually and then does not produce colic or encephalitis; and I know that is perfectly safe to do in a man like this, providing you gradually increase the medication daily over a period of ten days. It is best to give a low calcium diet for three days to which is then added ammonium chloride—3 Gm. the first day increasing the amount 1 Gm. a day up to the 7 or 8 Gm. tolerance.

I am very intrigued by the use of sodium citrate, which was first suggested by Dr. Seymour Kety when he was a medical student at the University of Pennsylvania. It was a very clever suggestion, because he showed that lead citrate was not ionized, just the way calcium citrate was not, in the blood plasma, and he assumed that because it was not ionized, it ought to be physiologically inactive. He gave large quantities of sodium citrate; the colic and pain disappeared and, at the same time, lead excretion increased.

DR. BAUER: I should think all the citrate ion would be destroyed in the gastro-intestinal tract.

DR. AUB: Much of it is, and of course that is one criticism of the work, but citrate output can be doubled with great ease by giving sodium citrate, and it doesn't take a high concentration in the plasma to make the lead nonionizable. It is an excellent idea which deserves a good deal more investigation. The other possibility that needs investigation is the use of BAL (British Anti-Lewisite) in the treatment of lead poisoning. It has not had a good trial. Those two forms of medication I think, look more promising theoretically than the use of the low calcium diet and ammonium chloride, because they may increase the rate of excretion and at the same time not increase the possibility of further symptoms, because the lead should be physiologically inactive.

DR. BAUER: How soon would you delead this man? And what regime would you have him on in the intervening period?

DR. AUB: If you want me to be dogmatic, which I do not like to be, I would keep him on a high calcium diet for three days after all pain stopped, and then put him on a low calcium diet for three days without medication. At the end of three days, if everything were going well, I would give him 3 Gm. of ammonium chloride and gradually increase it up to seven or eight over a period of ten days.

DR. ALLAN M. BUTLER: Suppose in so doing you gave an encephalitis and an optic atrophy that really handicapped him for life?

DR. AUB: I would not give him that by this regimen.

DR. BUTLER: How do you know?

DR. AUB: Because it does not happen any more. That happens when low calcium diet and ammonium chloride in maximum doses are given suddenly to a person who has been flooded with lead. We found five cases of recurrence of lead colic and two or three cases of encephalitis precipitated by our therapy, but those were in the very early days of this therapy and after we saw that, and when we began doing it slowly, as I have just suggested, we have not seen a recurrence.

DR. F. DENNETTE ADAMS: If you watch such a patient and see something suspicious creeping up on him, couldn't you go into reverse quickly and keep out of trouble?

DR. AUB: Yes. If he started to get lead colic you would stop the ammonium chloride but you would not give a high calcium intake if you wanted to continue to delead him, because then you would refill the calcium stores in the bone trabeculae and subsequent deleading would be ineffective because these fresh calcium stores would be the first to be liberated.

DR. BAUER: Why wouldn't it accomplish the same thing with no hazard whatsoever to the patient just to let him give up his occupation and stay on a low calcium diet for a year or longer? And let it go at that? This complication doesn't take place very often, but this man obviously had lead in his circulating blood. If that lead is readily mobilized and you don't know how much will be mobilized with 3 Gm. of ammonium chloride because of the individual's variation, and you approach a point of toxicity, you may have a complication which may result in an irreversible lesion. What is to be gained by attempting to delead this man?

DR. AUB: I am not enthusiastic about deleading any more. I won't fight for deleading, even on this patient. I think this patient would feel perfectly well and get back to work in about half the time if you

delead him. But, I think eventually he will delead himself.

DR. JAMES H. MEANS: After a patient stops receiving any lead, simply has some tucked away in the bones, do you regard that as perfectly innocuous? Can that stay there for the rest of his life without injuring him in any way?

DR. BUTLER: Won't a case like this have lead in his bone cortex for the rest of his life?

DR. AUB: This man will always have lead in greater amounts than normal, more than he would have if he hadn't been delead. You cannot get rid of all the lead.

DR. WYMAN RICHARDSON: Does it do any harm?

DR. AUB: It may occasionally precipitate a colic. If he left the hospital and went on a good drunk and got pneumonia, the colic would recur.

DR. BUTLER: That is because he would then have delead himself the way you would like to delead him now.

DR. AUB: It is possible getting drunk would be more fun than getting ammonium chloride.

DR. N. B. SKANSE: Don't you think the mechanism of the intestinal pain could be due to a disturbance in the metabolism of the porphyrins? These patients excrete a lot of porphyrins and I would like to draw a parallel to the case of acute porphyria, where you don't have any lead deposits but you have this disturbance of the porphyrins.

DR. AUB: Yes, it may be that pain in lead colic is due to the porphyrins in the body. There is always an excess of porphyrins in lead poisoning, they are always excreted in the urine, and they do produce a colic very much like lead poisoning. It may well be. I have never done any research work on it. I would be unwilling to say that that is the reason, but it may very well be linked up with the colic. That is not the reason for the paralysis. The paralysis has been shown very nicely to be due to a poisoning of the adenosine-triphosphate mechanism with the inability to resynthesize it.

DR. BUTLER: You talk about the effect of intravenous calcium chloride being due to calcium. Are you sure it was? Do you know whether the same amount of calcium, given as calcium levulinate as would be given by calcium chloride, would have the same effect or is it due to the chloride?

DR. AUB: That is a question I am unwilling to answer.

DR. BAUER: I think we have some evidence that it is directly related to the concentration of the calcium salt and I think that is why this patient did not re-

spond. He received only 10 cc. of a 10 per cent solution of calcium levulinate.

DR. BUTLER: Then why do we use calcium chloride?

DR. AUB: Calcium chloride is more effective in stopping it than is the gluconate. I have not had any experience with the levulinate.

DR. BAUER: But I think only because there is more calcium per cc. than in the case of gluconate.

DR. BUTLER: Do we know whether the effect is due to the chloride or the calcium?

DR. FULLER ALBRIGHT: If the chloride ion is the important one, as suggested by Dr. Butler, sodium chloride should work. It cannot be the chloride.

DR. BUTLER: Yes, it could. The calcium chloride might do an entirely different thing to the serum.

DR. BAUER: In some of the cases we treated years ago if we gave the same amount of calcium in the form of calcium chloride or gluconate, that was the important thing.

DR. LEWIS K. DAHL: It seems to me if that is true you should always give calcium gluconate, because the chloride is an acid-producing salt and so it would pull out more lead from the bones.

DR. BAUER: You give only 20 cc.

DR. ALBRIGHT: It is only by mouth that calcium chloride is acid-producing.

DR. BUTLER: How soon does the calcium get out of the circulation and leave the chloride—do we know? I cannot believe the calcium stays in the circulation very long.

DR. AUB: You don't give enough to produce an acid reaction.

DR. BERNARD M. JACOBSON: Is it known whether this patient had any break in his industrial hygiene? Why did he come down with lead poisoning and his fellow workers apparently not?

DR. BAUER: That we don't know. The report from the Industrial Hygiene Medicine Section in the State Department of Public Health is very good. They say this particular industry or this particular firm is well aware of its industrial hazards, they have been very conscientious in putting into effect good ventilation, providing respirators, etc. There was no one else at the time. It would look as though it was the patient rather than the industry. On the other hand, if he doesn't have a good respirator, if he is careless in using it, if he is an individual who is more sensitive to lead or more prone to develop lead poisoning than the fellow next door to him, those factors may operate. Certainly we have seen people who have worked in the Hood Rubber mixing room for twenty years and have never had lead colic. Someone comes in and in three months he has acute lead poisoning, with or without complications such as encephalitis.

DR. AUB: Other men in this factory had their appendices out in the last six months.

DR. BAUER: He retracts that story after being pushed.

DR. MEANS: Was the enema given before or after you made the diagnosis of lead poisoning?

DR. BAUER: The diagnosis of lead poisoning was made but they wanted to be sure he did not have intestinal obstruction, and the Surgical Service, I understand, has charge of acute abdominal cases, and they insisted on the enema.

DR. DAHL: He came into the Emergency Ward during the hours when the Surgical Services see all patients first.

DR. MEANS: Did they know he had lead poisoning?

DR. DAHL: I believe they did, yes.

DR. MEANS: They don't need to worry about keeping him on the surgical side. As soon as a fellow has lead poisoning, the chances of his having some surgical condition plus lead poisoning would be about one in four billion, I should think. I think it should be emphasized: This is, I gather, a rare disease. It used to be very common. We were all very familiar with it. We would not have missed the diagnosis under any circumstances, but the younger people may not think of it or recognize it when they see it. Sometimes an old appellation is useful in diagnostic thinking and I always think the 'old expression of "dry gripes" is an excellent one for this ailment. If you think of it in that term, you can never miss it, *probably*.

DR. BAUER: I think the other important thing to remember in a case like this, where you have good evidence of lead poisoning is that if you give sufficient calcium intravenously and obtain complete relief, you can rule out inflammatory lesions which can produce colicky pain of the type this man had, because calcium chloride will not give relief in the case of gallstones with associated inflammation, or other types of colic. Where it is an uncomplicated gallstone colic, you will get relief. I think in this instance more use could have been made of calcium chloride, also the instituting of a more prompt and complete treatment, and we could have foregone the pleasure of a barium enema.

DR. ALBRIGHT: It will stop a colic other than that.

DR. BAUER: What type of colic?

DR. ALBRIGHT: If he had a perforated duodenal ulcer.

DR. BAUER: I have never seen it happen.

DR. MEANS: I should think if a fellow had severe dry gripes and a lead line and stippling, you would not have to worry much about other diagnoses, and then if you found he worked in a storage battery factory . . . !



DR. BAUER: During the year that Dr. Aub had Ward 4 filled with patients with lead poisoning there were two people with recurrent abdominal symptoms both of whom turned out to have subacute perforating-duodenal ulcers.

DR. ALBRIGHT: And calcium chloride would relieve their pain too.

DR. BAUER: I don't remember that calcium chloride was effective in those cases.

### *Editor's Follow-up Note*

On follow-up visits to the Medical Outpatient Department on the 14th of February and the 14th of March this patient was found to have been completely asymptomatic, and on his last visit was planning to return to work in a new occupation.

### CASE 14 -

#### SUBACUTE BACTERIAL ENDOCARDITIS

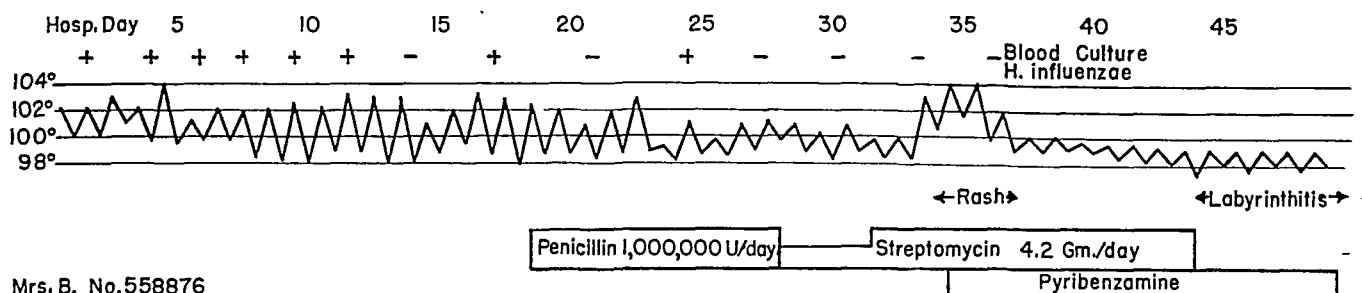
DR. EDWARD F. BLAND: It has been the rather firm conviction of the house staff that now and then it might be worth while to consider in these sessions a single disease entity in a somewhat comprehensive fashion. Such is our plan today and we are very grateful to Dr. Palmer and his half of the service for allowing us to encroach upon their time a bit. Today we are concerned with subacute bacterial endocarditis and we are presenting a patient who poses a very serious therapeutic problem. Dr. Peterson will present it.

DR. EDWIN W. PETERSON: Mrs. B., No. 558876, is a 32-year-old, white, married, housewife who came into the hospital on January 2, 1947 with a diagnosis of subacute bacterial endocarditis. Her chief complaint at the time was an evening elevation of temperature for about two months. At the age of five she had an attack of acute severe, migrating polyarthritis which was diagnosed as rheumatic fever, and after which she was subsequently told she had a damaged heart with a leaky valve. She had no symptoms from this, however, except for some dyspnea on extreme exertion, and her only limitation was that she could not participate in athletics. She was in good health until 15 months before admission, when she began to lose weight. There was no loss of appetite at the time, but anorexia did appear after several months, and over that time she lost a total of 40 pounds. There was no precipitating factor that could be elicited as to why this loss of weight started at that time. She had no minor surgery, no infections of which she knew, and only had some teeth filled the month before. Last October she went to the Pratt Diagnostic Clinic because of some vague epigastric pain coming

on after meals and relieved by belladonna. They did a gastro-intestinal series, chest films, plain film of the abdomen, and electrocardiogram and BMR. All of these were normal. However, her spleen was felt at that time and because of some questionable petechiae they took five blood cultures. These all were sterile. However, she was advised on discharge to check her temperature every evening, which she did, and two months before admission, in the latter part of November 1946, she had a spike of 102°. She went to bed at that time and has been there ever since. Over that two months' time she spiked an evening temperature between 99° to 102° by mouth and, despite the slight anorexia and feeling of feverishness she felt so well that she refused to come into the hospital, despite the begging of her local doctor. During the last two weeks in November she was started on a course of penicillin in oil, 300,000 units a day for two weeks. At the end of that time there was no response, so her doctor increased the dosage to 600,000 units a day for one week, and still got no response. Three further blood cultures were negative at that time.

Finally she became convinced that she was really sick and came into this hospital. On admission she was very pale, she had petechiae on her palate, buccal mucosa and under the tongue, as well as a fading spot on the right hand. She had a fever of 102°, pulse 90, respirations normal. Her chest was clear; her heart was enlarged about a centimeter beyond the mid-clavicular line and auscultation revealed both systolic and diastolic murmurs at the base and apex. Her abdomen was negative except for a spleen which could be felt 1 cm. below the left costal margin. Some observers thought that early clubbing of the fingers was present. Her white count was only 7,000 on admission; hemoglobin 10.7 Gm. by the Sahli method, and she had a negative urine.

She ran a febrile course while under observation and we felt very sure she had subacute bacterial endocarditis. She had numerous blood cultures taken, between one and two a day, during the first three weeks she was here. However, the bacteriology laboratory reported only occasional contaminants and did not give us any lead as to the pathologic organism which was the cause of her fever. Therefore, on the 21st hospital day, we decided to start the trial of penicillin in the hope that we might be able to hit the infection. This was done with a dosage of one million units a day by constant intramuscular drip. There was no immediate response, and several days after we had started this treatment the bacteriology laboratory reported that six flasks had come down with a small gram-negative rod which, although they had looked upon it as a contaminant at first, was now



Mrs. B. No. 558876

felt to be the offending organism. Due to the fact they thought it might be a pleomorphic streptococcus, it was decided to continue penicillin. A few days after that they identified the organism as of the *Hemophilus para-influenzae* group; streptomycin sensitivity revealed that the organism was inhibited in a concentration of only two units of streptomycin per cc. Therefore, on the 29th hospital day she was shifted to streptomycin and given a dosage of 2.4 Gm. a day, which gave a level of between 12 and 16 units per cc., eight times the level necessary to inhibit the organism in the laboratory. Penicillin was discontinued at that time.

DR. BLAND: The patient has developed overnight certain complications which make her quite uncomfortable, but she is presentable and we will show her in a minute. Before we do so, I would like to say just a word about streptomycin in connection with bacterial endocarditis. We believe the diagnosis here is established. Certainly she has it clinically, and we believe the bacteriologic evidence is sound. I might state that when we were having difficulty getting positive cultures we resorted both to arterial blood and sternal marrow cultures, but the organisms were finally grown from the venous blood.

This is an unusual case of para-influenzal endocarditis. We have had one other similar case which I would like to mention briefly. A girl of nine at the House of the Good Samaritan had been ill for four months with a swinging fever of this nature. Her gram-negative organisms were easily cultured and were studied by various people including Dr. Maxwell Finland. An exact classification was difficult, but they were considered para-influenzal in nature. That patient failed to respond to penicillin. We then started her on 2 Gm. of streptomycin a-day but had to give it up at the end of seven and one-half days because of inadequate muscles. She developed severe local reactions. In addition, she ran a vigorous fever. We were quite disappointed that we had to discontinue the therapy, but when we stopped, her fever subsided promptly and she has been well ever since. That was last fall (six months ago).

Here again we are dealing with a gram-negative organism of similar nature and we probably have only one opportunity, with streptomycin, of arresting this infection. If we undershoot the mark at first, it is probable that these organisms will increase their resistance promptly and strikingly. I hope Dr. Finland will correct or amplify these statements in the light of his experience. Therefore, we believe that this is our only chance and, hence, we increased the streptomycin to 4.2 Gm. a day; this is a sizable dose. We do not yet know the blood level with 4.2 Gm. a day, but the blood level with 2.4 Gm. was 16 units versus a resistance of two for the organism. This represents a fair margin of safety.

The difficulty with streptomycin, of course, is two-fold. First, the organisms are apt to become resistant unless the dose is adequate; and secondly, complications are more troublesome than with penicillin, chiefly skin rashes, pruritus, fever, and in those who get the drug over a longer period of time, labyrinthine disturbances. Dr. Donald King, who has had some experience with this drug in tuberculosis, tells me that when the labyrinthitis occurs, it is apt to be irreversible. Fortunately, the drug has to be given longer than three weeks, I believe, before this more serious complication appears.

With these points in mind, we have increased the streptomycin to 4.2 Gm. a day. Two days ago she continued to run a fever, but of a slightly different character from her previous pattern. We were not particularly concerned about this because we expected it with streptomycin. Actually we thought it might be favorable since the temperature swing was less than previously. Two days ago she complained of itching and there was a slight transient papular rash which disappeared in one-half hour. Yesterday it was a little more extensive on her arms, it itched and her temperature was higher. We continued the drug as before, and this morning she awoke in acute discomfort with a severe pruritus and a generalized florid papular rash of rather alarming appearance and a temperature of 104°.

In spite of this new development we believe the

continued use of streptomycin is our only chance of arresting her infection. We would hate to stop the drug quite yet, even though she has been on it for nine days. The danger, as Dr. King pointed out to us, is now exfoliative dermatitis, which occasionally has occurred, but fortunately is rare. Early this morning she received 50 mg. of Benadryl and within an hour she was much better; the itching had almost disappeared, her temperature had begun to drop, and the last report is that it was 100°. So it looks as though we may be able to control the situation with Benadryl and still continue the streptomycin.

Mrs. B. whom you see here is a most co-operative patient. She was extremely uncomfortable two hours ago; she could not lie still in bed because of the intense itching. When I saw her again a few minutes ago upstairs she told me she was much more comfortable and you can see she is lying quietly now. Perhaps you can see from your seats this extensive papular rash. It is definitely less florid by about 100 per cent since we started Benadryl.

Throughout her long illness Mrs. B. has had surprisingly few symptoms. She describes very characteristically the red spots which she had in her fingers and toes before coming here. There has been none recently. Her spleen, if you will recall, was palpable last October. Also in addition, her sedimentation rate was rapid at that time. That laboratory finding also disturbed the other hospital a little and was an additional reason why they took a considerable series of blood cultures at that time.

We are very pleased that Dr. Finland could come today to tell us about streptomycin in relation to this situation and to other infections in general. Dr. Finland, would you comment on this case?

DR. MAXWELL FINLAND: This patient illustrates many interesting points. There are also many features of streptomycin therapy that still need elucidating, in spite of the large literature which is rapidly accumulating.

The other case that Dr. Bland mentioned is rather unique, I think, because we have not been able to find any reported cases of gram-negative bacillus endocarditis that have recovered definitely as a result of streptomycin therapy. The only case that was reported, one from the Presbyterian Hospital in New York, was first treated with sulfonamides and penicillin and was in a bacteria-free state for some time and was also afebrile when streptomycin was started, so it is difficult to say for certain just what streptomycin had to do with the recovery in that case. The other cases which have been reported, interestingly enough are cases of subacute bacterial endocarditis due to

streptococci which had failed to respond to penicillin but which on test proved to be more sensitive to streptomycin than to penicillin. There were two instances, I believe, in which the organism was sensitive to 8 units of penicillin in contrast to 1 or 2 units of streptomycin. There was another instance in which it was stated that the organism was sensitive to 0.1 unit of streptomycin. We haven't found such sensitive organisms yet. A strain requiring 8 units of penicillin is quite a resistant strain, as we consider penicillin sensitivity, but when we consider 8 units in terms of streptomycin, that would be considered a moderately sensitive organism. Nevertheless, 8 units of penicillin would be about 5 micrograms because a unit of penicillin is 0.6 microgram. The unit of streptomycin is 1 microgram, and there are very few varieties of organisms sensitive to less than 5 units of streptomycin. Some of the influenza bacilli (*Hemophilus influenzae*) are sensitive to between 0.5 and 5 units. They are among the more sensitive. *Pasteurella tularensis*, the organism that causes tularemia, is among the most sensitive and may be sensitive to between 0.1 and 0.5 unit. Some strains of Friedlander's bacilli are inhibited by about 0.5 unit, but most of the organisms with which we deal—like *E. coli*, *B. proteus*, and *B. pyocyaneus*—require somewhere between 5 and 50, or even 100 units or more in the case of *pyocyaneus* organisms.

There is another factor which is very important to bear in mind when we talk about sensitivity to streptomycin but which we do not have to think about when we talk about sensitivity to penicillin. In general, the test tube measures the sensitivity of penicillin fairly well if we compare that with the way the patient responds, but the same cannot be said to be entirely true of streptomycin. There may be several reasons for that. In the first place, the sensitivity of the organism in vitro is very markedly affected by the pH of the medium—you can alter the sensitivities between 2- and 50-fold within a range of pH between 6.0 and about 8.0. Now, that is a big difference and may necessitate levels outside of the possible range of dosage. The practical range of streptomycin dosage is much smaller. Also, in the case of tests for penicillin sensitivity, you do not worry too much about the number of bacteria in the inoculum, because any given concentration which will inhibit bacteria will inhibit numbers over a wide range, perhaps more than a 100,000-fold range, whereas 10- to 100,000-fold range in the numbers of organisms in the inoculum when we test for sensitivity to streptomycin may mean 2- to 16-fold difference in the result. That again may mean concentrations greater than those

obtainable within the range of dosage that it is possible to administer. So that if we say that an organism is sensitive to 0.5 unit streptomycin and we can find 5 or 10 units in the blood, we are really fooling ourselves if we think that we have a 10- or 20-fold margin of safety, because we don't know just what the sensitivity of the strain is in the particular location in the body where we want to make it work.

In a patient with bacterial endocarditis if we consider the organisms which float around in the circulation, I don't think we need streptomycin, because the body can usually take care of them anyway. We can prove that in subacute bacterial endocarditis due to *Streptococcus viridans*. When we draw the patient's blood for culture we can usually grow about 50 organisms per cc. of blood in agar pour plates. If now we take 1 cc. of that same fresh blood, defibrinate it together with its 50 organisms and add up to one million organisms from another culture, grown from the same patient, that blood will sterilize itself completely and rapidly. The same may be true in the present case. On the other hand, when we take the valve, which may contain large pure colonies or groups of colonies of bacteria, then we have a different situation locally in the vegetation. The same reasoning can be applied to the situation in local abscesses. It would seem then that the test tube does not always tell us quite what we want to know.

There is still another point I might mention that might have a bearing specifically in this case, and that is in relation to dosage and the spacing of the individual doses. We have had a very practical problem at the City Hospital of not having enough nurses to carry out all the therapy we would like to give our patients, and so we tried to arrange things so that we could get a little more of what we order and limit our requests to essentials. If we ordered penicillin to be given every two or three hours to many patients, we found that some patients often did not get all of the doses ordered. So we thought it might be better if we gave fewer doses and larger amounts each time. We have found that by increasing the total daily dose by some small or moderate increment, we could give penicillin successfully at eight-hour intervals in many cases. In treating pneumonia, for example, we are using 100,000 units every eight hours. I think that amount is far in excess of the minimum effective amount that the vast majority of patients need, and clinically we get as good results and perhaps better results than before, if that can be judged casually.

In the case of streptomycin we have better justification for prolonging the intervals, because streptomycin is excreted somewhat more slowly, and we give

much larger amounts. We give only 100,000 units of penicillin. That would be a pretty small dose for streptomycin, yet it is only 0.06 Gm. of penicillin, whereas we are accustomed to giving streptomycin in grams—that is, we usually give streptomycin in doses of 1 Gm. every six hours. Now with 1 Gm. every six hours, one can usually obtain a level of 10 to 20 units (or micrograms) at the end of the six-hour period. That is about as high as we can hope to get and still keep the patients fairly comfortable. Even four doses a day is quite a lot, but four doses is two less than six doses, and where each site of injection is something that the patient remembers for more than 24 hours, we would like to reduce the number of injections somewhat if possible. The patients begin, after a couple of days, to get localized swelling and redness and often get generalized aches and pains; and when we gave 6 Gm. a day, these manifestations were quite marked. Possibly doses of 0.5 Gm. every three hours would give less local reaction with each injection, but the patient will soon tire of the injections.

We have had several cases of para-influenza bacillus endocarditis since I have been at the City Hospital and none of them survived. There is one point that might be raised about that organism in relation to this case, and perhaps in relation to the general problem of bacterial endocarditis. The first case of bacterial endocarditis that was treated at the City Hospital by Dr. Keefer was a patient with type 19 pneumococcus bacteremia. He never did show a complete response, but the type 19 pneumococcus cleared rapidly from his blood stream, only to be replaced by *B. pyocyaneus*. It is possible that in the present case we were dealing originally with another organism, perhaps one of the classical subacute bacterial endocarditis strains of *Streptococcus viridans*, judging from this long history, and now we have a different strain which has infected this patient and which has blossomed out because the treatment which she had with penicillin in beeswax and peanut oil may have eliminated the streptococcal infection only to have it replaced by the present one. Or perhaps it was a mixed infection from the start.

One can argue the question as to whether you need to have any stated blood level throughout the entire period of treatment, that is, the entire interval between doses. There are those who believe that what we are interested in is a dosage which gives you high peaks, because the penetration into or through serous cavities or through the walls of abscesses is conditioned by the concentration around that membrane or around that wall. Now if you have a very high concentration, more of it will get into that cavity and

then it will be somewhat slow in coming out. On that theory one would consider that the treatment of a focal infection would be directed at trying to get many or several high peaks rather than maintaining a constant level which one thinks is suitable for the sensitivity of that particular strain. In other words, in the case of penicillin treatment, perhaps 300,000 units given every eight hours is better than 100,000 units given every three hours, let us say, or something in that order. In general, the peak level and the period after a dose during which any given level is demonstrable varies with the size of the individual dose. A 200,000 unit intramuscular dose would give you a measurable level in the case of penicillin up to, say, six or eight hours, but a 25,000 unit dose would give you such a circulation level for only about three hours. And the peak at the higher dose may be perhaps eight times what we get with the lower amount. I don't know how much the eight-fold difference makes in the penetration, but it must make considerable difference, and that is really what we may want in some of these cases.

In relation to the rash, I think it is interesting that it appeared at the classical time. One gets rashes from sulfonamides or from penicillin most frequently at the end of the first week or from then on. I think it is worthwhile pointing out, however, that when you have a generalized rash with itching, the danger of getting other serious sensitivity reactions and even exfoliative dermatitis is fairly good if you continue the treatment, even though the latter is an infrequent occurrence. The particular type of rash that this patient shows is more likely to give it, I think, than the type in which there are only a few papules with fever. We have also had instances, just like the one Dr. Bland mentioned, of streptomycin-treated patients who went along and had increasing fever during treatment of urinary tract or other infections and then had a sharp drop in the fever promptly after the treatment was stopped, even when there was no rash, and clinical recovery followed rapidly thereafter. Of course, if you have negative bacteriologic findings, it is easier to ascribe this effect to the treatment. I would agree that in this case we are dealing with a desperate situation where you really have, perhaps, a last chance.

There is one more interesting point that I might make here or speculate on a little. "Hitting organisms hard" at first is thought to be the solution to the resistance problem. But one cannot hit organisms hard with streptomycin in the patient, because the difference in concentration of streptomycin in the blood obtained with doses ranging between 2.4 Gm. and 4.0 or 6.0 Gm. is very small in contrast to the

thousand-fold difference in resistance that may develop in 24 hours in some cases.

DR. BLAND: Thank you very much. To most of us, this is new territory which we are exploring. Specifically, in this case would you feel that we should continue for perhaps a few more days or is that too risky?

DR. FINLAND: I think that would be contingent upon how much you can keep her free of symptoms.

DR. BLAND: If she gets a good response to Benadryl, you would be inclined to continue with the course for, well, we tentatively planned on two weeks. Is that long enough?

DR. FINLAND: Well, we like to treat them almost like we treat tuberculosis. Not quite. That is the way we treat subacute bacterial endocarditis with penicillin. We would like to have them bacteria-free for three to six weeks. But, obviously, that desideratum is not possible in most of our cases. In cases of tuberculosis, where the average dose is about 1.8 Gm., apparently it is possible to treat for months at a time and you get a few cases that develop complications, but you treat only the type of case where that is only of minor importance, and the patients adjust to the labyrinthitis after a while. They can learn to walk. They have a hard time for a few weeks, but they will learn to walk—presumably they do not get any recovery of the nerve injury, but they get recovery of function. That is not really so terribly important and certainly would not be important in a case of this sort.

DR. BLAND: Would you be inclined to reduce the dosage and carry it for a longer period or should we not?

DR. FINLAND: Well, I would reduce the number of injections, certainly.

DR. BLAND: She is getting it every four hours.

DR. FINLAND: You can give it to her every six hours and get just as good results. We give 1 Gm. in about 5 cc., that makes a pretty thick solution, but also it does not give you the large distension of muscles and therefore, perhaps, cuts down the irritation.

DR. ALLAN M. BUTLER: Are you sure that you are causing less pain to your patient by giving 1 Gm. every six hours than you are by giving 0.5 Gm. every three hours?

DR. FINLAND: Well, I think that is debatable, but I think the problem of coming back every three hours really is a problem, which from personal experience, I think is best avoided. Especially with something of this sort. The pain is somewhat less, surely, with each individual injection. Probably also the rather tender nodules that we see would be much less frequent if we gave smaller injections.

DR. BLAND: In that connection, fortunately, this patient has been markedly free of local reaction. She has had some, but not bothersome. We are a little bit handicapped in following the blood, because it is extremely difficult to culture the organism, even at best, and so when we get negative cultures we are uncertain as to where we stand.

In view of the reaction, would she be less apt to have that if we were at this level for another few days and then, perhaps, a week or two at 1.8 Gm. or something like that?

DR. FINLAND: I am not certain.

DR. BLAND: You think the dosage has little to do with this type?

DR. FINLAND: Within this dosage range I am not sure whether that would make a difference. With increasing dose you probably get an increasing chance of getting all of the reactions, including labyrinthitis. I am not sure there is more evidence about the labyrinthitis than there is about the rash.

DR. BLAND: You think to stop therapy at the end of two weeks might be a little bit risky?

DR. FINLAND: I think that that will solve itself. You probably won't be able to continue to give it that long.

DR. BUTLER: How about giving such a thing as novocain, as we did with penicillin? Does it help with streptomycin or not?

DR. FINLAND: It hurts just as much when it is going in.

DR. BUTLER: Yes, but afterwards?

DR. FINLAND: If you give it with the streptomycin, most of the pain you have is while it is going in and that is not relieved by the mixture with novocain. What you relieve is the subsequent pain for a short time. Well, the two times when you have pain in these injections are, one, when it is going in, and the other is over a period of many hours, so I don't think that that solves the problem very well.

DR. JACOB LERMAN: I would like to ask Dr. Finland if it were possible to start off with a small dose of Benadryl or Pyribenzamine, not the full 50 mg. dose, but 10 mg. as a preventive, starting it simultaneously with the administration of streptomycin and avoid the sensitivity reaction and the danger of dermatitis.

DR. FINLAND: I cannot answer that question, but I doubt it.

DR. LERMAN: It can be done with other types of reactions, such as serum sickness.

DR. FINLAND: It is possible, but some people, of course, will develop reactions to the Benadryl.

DR. LERMAN: That is the reason I think Pyrobenzamine is better.

DR. FINLAND: I have had no experience with that.

DR. BLAND: We have had experience with one somewhat similar situation, a doctor who had Streptococcus viridans bacterial endocarditis who very promptly on penicillin developed angioneurotic edema, in fact a little laryngeal edema, and we stopped promptly, gave him Benadryl, then slowly resumed the penicillin; he was able to finish a course and he has been cured completely.

DR. FINLAND: One point may be raised here, and that relates to the brand of streptomycin being used. The brands of streptomycin have varied recently about as much in purity as the penicillin products varied, let us say about two years ago. Good and pure streptomycin is a dry, fine powder. It is almost white, and isn't caked up at the bottom or along the sides of the vial. Each gram will dissolve in about 5 cc. of distilled water or isotonic saline, though it may not stay in solution at that concentration. Some of the preparations which are less pure have various colors in them and are amorphous, sort of caked. The latter kind has given more severe and more frequent reactions, particularly the local irritation at the site of the injections.

DR. BLAND: Dr. King, you have had a lot of experience with streptomycin in tuberculosis.

DR. DONALD S. KING: Our only experience is based on 21 cases under treatment now for almost four months. They have had 0.3 Gm. six times a day, that is 1.8 Gm. a day. One of those 21 developed this very severe exfoliative dermatitis and we almost lost him, but that is the only case out of 150 being treated by the Veteran's Hospital, which has had this skin reaction and had to have the streptomycin stopped. They all get dizzy in the fourth week, they probably lose their labyrinths, and I think they have permanently lost them, so far as we can tell. The cerebellum is supposed to take over. They do not walk as well on a rough surface after dark, but I doubt whether that is a reason for not giving it. It is a reason for not giving it in minimal tuberculosis, I would say.

DR. BLAND: Have you any advice to give us as to proceeding from here on? We hesitate to give up the drug, I believe, quite yet, unless we are forced to.

DR. KING: The way this woman reacted to Benadryl, I don't think she is going to be one of the exfoliative type. This other man made no response to Benadryl; he went on and became very ill quite quickly.

DR. BLAND: Her appearance within an hour is quite different from what it was earlier this morning, and her fever is almost lower than it has been at any time. Not quite. Perhaps we can continue the drug for a while yet, and make the decision as the circumstances arise.

We had rather planned today to crystallize our experience in bacterial endocarditis. In many ways it has been remarkable when you consider that four years ago it was almost a uniformly fatal disease. Perhaps four of five per cent responded to sulfa or heparin or the various combinations, or surgery on a patent ductus. The experience here with some 45 cases in the penicillin era has really been extraordinary. Dr. Paul has these matters right at his fingertips. I wonder if he would summarize it briefly in the few remaining minutes?

DR. OGLESBY PAUL: We have had experiences with 44 cases of subacute bacterial endocarditis treated with penicillin, at this hospital during the past three years. A few general remarks may be made about this group. The patients ranged in age from  $3\frac{1}{2}$  years to over 70. As would be expected the majority had underlying rheumatic heart disease, with the congenital group comprising one-seventh of the total number. Non-hemolytic or alpha-hemolytic streptococci were the offending organisms in more than 80 per cent of this series, and fortunately most of the strains were very to moderately sensitive to penicillin. In three cases, the resistance was very high and therapy extremely difficult, massive doses being required. Approximately three-quarters of the group may be considered as bacteriologic cures, with quite satisfactory follow-up data now available.

DR. BLAND: The approximately 70 per cent cure is truly an encouraging figure, and it is even more impressive when we realize there were actually only two patients in whom the infection itself failed to be controlled. We have had two patients who received "massive" penicillin therapy of approximately ten million units per day. One was the famous Mr. W. who by reputation is well known to most of you, and the other was a patient of a few weeks ago. We considered ten million a day a massive dose. However, Dr. Loewe in New York, in reply to a letter states that he has had five patients who have received 40 million units a day, one of them receiving a total of four billion units of penicillin in addition to 36 Gm. of streptomycin. Of these five cases, three recovered and two died.

#### FOLLOW-UP TWO WEEKS LATER

DR. BLAND: As you remember, this patient had a vigorous reaction with rash, marked pruitus, and so forth. She responded dramatically to antihistamine therapy, Pyribenzamine. We continued the large doses of streptomycin for 16 days and we planned on keeping it up for three weeks. On the 15th day dizziness appeared, evidence, we thought, of early

labyrinthitis. The drug was stopped on the 16th day. The labyrinthitis was and is definite. The disease, we believe, has been arrested and we hope cured. Clinically she is much better. She looks better, her sedimentation rate is just beginning to recede and all cultures since the institution of streptomycin have been negative. It is of some interest that we were able to continue the streptomycin with an antihistamine drug. The only thing in connection with the therapy which we have proved, which I think may not have been known before is that the antihistamine drug will not prevent the serious complication of labyrinthitis.

DR. BERNARD M. JACOBSON: Is the labyrinthitis still active?

DR. BLAND: No. The labyrinthitis is not active as such, but she has no equilibrium. Her cerebellum is taking over, we believe; she is up and around. She has difficulty in maintaining her balance when she is going about, but the active stage has subsided.

DR. JACOBSON: May I make a suggestion about labyrinthitis. There must be something in the literature about it, but I thought it was original when I first discovered it. A year ago, I saw a patient with ordinary Ménière's syndrome, etiology unknown. He could not get up without dizziness, nausea and vomiting. He looked pale and I wondered whether he might have some vasoconstriction going on in his labyrinth. I gave him amyl nitrite; he had the nitrite reaction, shook his head and said the dizziness was gone. I had him get up and walk around and for the first time in days he could do so. I kept him on nicotinic acid, 100 mg., five times a day for the next three days. The dizziness did not recur. Since then I have used it in four other cases with very similar striking results. I suggest using an acute vasodilator like nitrites, possibly followed with more protracted vasodilator such as nicotinic acid, not the amide, but plain acid.

DR. BLAND: We shall try it. I doubt at this stage that it will be helpful.

DR. JACOBSON: No.

DR. BLAND: Because the labyrinth, we believe, is gone. It is now a question of adjusting the cerebellum.

#### Editor's Follow-up Note

This patient was discharged from the hospital on the 27th of February, 1947, at which time ten consecutive blood cultures had been returned as having shown no growth following the institution of streptomycin therapy. She was ambulatory but she was still unsteady due to labyrinthine involvement. She will be followed in the Medical Outpatient Department.



# WHAT'S YOUR DIAGNOSIS?

This 57-year-old white male was admitted to the Medical Service on March 22, 1940 for the first time. He was extremely weak and the history was difficult to elicit. Weakness and fatigability had begun approximately eight or nine months before. He had noted a yellow tint to the skin and sclerae during the same period and thought that he had had a low-grade fever. He had experienced several chills, but did not remember how frequent they had been. He had noted tarry stools while taking iron which had been prescribed by his physician who told him that he was anemic and had heart trouble. Digitalis had been taken daily for three weeks before admission. He was occasionally bothered by pains in both hands and feet. There had been transitory edema of the feet and ankles. Several small nose bleeds had occurred but he had had no bleeding tendencies elsewhere. There was a family history of epistaxis. Bilateral flank pain associated with red urine had occurred several times during the present illness. There had also been some dysuria and stranguria. During the few weeks before admission increasing exertional dyspnea with frequent attacks of paroxysmal nocturnal dyspnea had been prominent symptoms. He was averaging three morphine injections daily for the relief of dyspnea. Vague precordial pains of a transitory character had been noted. There had also been slight nausea with vomiting on several occasions. He had vague abdominal discomfort in both the upper and lower quadrants a good deal of the time. Visual scotomata were also noted.

The past history was of interest. He had a painless penile lesion 31 years before and was treated with 10 to 15 intravenous injections. Seven years before he had an attack of renal colic with oliguria, nocturia and dysuria. He had a similar attack two or three days before admission. He had experienced frequent attacks of syncope, vertigo and visual scotomata. He had had some difficulty in walking at night. At the age of 17 he had had gonorrhea at which time he also had an attack of polyarthritis. One examiner stated that this was a migratory polyarthritis; another stated that it was not migratory. For 18 to 20 years there had been mild ataxia, numbness of the feet and legs and sharp pains in the knees.

**Physical Examination.** Temperature 97°, pulse 64, respiration 16, blood pressure 140/50. He was a lethargic, weak, malnourished, slightly orthopneic man with a yellow sallow color to his skin. There were numerous red petechial spots over the left side of the face and over the trunk. A few small nodes were felt in the anterior cervical and inguinal regions. The mucous membranes were very pale. De Musset's

sign was positive. On one occasion the pupils were dilated and did not react to light. Later they were constricted and still did not react. The retina and vessels were very pale. Numerous flame-shaped hemorrhages, some with white centers, were scattered radially around the optic disks. There was no papilledema. Bleeding points with dried blood were seen in the nose. The mouth was edentulous. Petechiae were present on the hard palate. A slight venous distension was noted in the neck. The thyroid was not enlarged. A tracheal tug was present. Carotid artery pulsations were overactive. The chest was increased in the A-P diameter. The lungs were clear. The heart's point of maximal impulse was seen and felt in the fourth and fifth interspace 2.5 cm. outside the midclavicular line. It was forceful and thrusting. There was a systolic shock but no thrill. In the mitral area there was a rather blowing, low-pitched systolic murmur, well transmitted into the left axilla  $M_1$  was loud and occasionally reduplicated. In the aortic area there was a definite systolic and diastolic blowing low-pitched murmur, the systolic phase being the longest and followed by a rather short diastolic diminuendo blow. This was transmitted down the left sternal border.  $P_2$  was greater than  $A_2$ . The systolic blow was heard well in the neck. The right border of dullness was increased 2 or 3 cm. in the second interspace. Rate and rhythm were normal. Blood pressure 140/50 in both arms. A pistol shot was audible over the brachial and femoral arteries and Duroziez's sign was present.

The abdomen was relaxed. The liver and spleen were not felt. There were no ascites or masses. Slight bilateral costovertebral-angle tenderness was present. The descending colon was readily palpable. Genitalia were normal. There was generalized weakness and atrophy. Knee and ankle jerks were bilaterally absent. Vibratory sense intact in lower extremities. Reflexes were normal in arms.

## LABORATORY DATA

Urine				
Date	Sp. Gr.	Reaction	Albumin	Microscopic
3/22	1.014	Alk.	+1	Numerous WBC and bacilli; 1-2 RBC
3/26	1.016	Alk.	+1	Innumerable WBC, RBC and bacilli
3/28	1.014	Alk.	Trace	10-15 RBC; 10-15 WBC
3/31	1.014	Alk.	Sl. tr.	20-25 RBC; 5-6 WBC

A total of 23 urine examinations continued to show microscopic hematuria and white blood cells. Gram smears of the urine sediment revealed "Large gram-positive diplobacilli and streptococci." The urine was persistently negative for bile and acetone. Urine cultures yielded nonhemolytic streptococci, gram-negative bacilli and *B. morgani*.



**Blood**

Date	RBC (million)	Hgb. (Gm.)	WBC	Ju.	Stabs.	Segs.	Eos.	Bas.	Lymph.	Mono.	Myel.	Blasts
3/22	1.02	3.7	5,040	2	0	62	4	0	24	2	2	0
3/25	1.76	6.2	1,200	2	5	33	3	1	43	4	0	1
3/26	1.50	6.0	1,750									
3/27	1.40	5.8	1,100	0	6	36	2	0	44	6	0	0
3/28	1.50	5.0	900									
3/29	1.78	6.8	850									
3/31	2.10	6.3	1,200	0	2	5	0	0	74	5		
4/1	1.65	6.4	1,500		2	9	0	0	80	6		
4/6	2.30	7.8	1,400			14	0	0	68	4		
4/9	3.10	10.8	700			16	0	1	71	4		
4/16	3.75	12.2	1,800		1	17	0	0	74	2		
4/22	2.65	8.2	720		2	22	0	0	64	4	2	

Blood smears consistently showed moderate anisocytosis, poikilocytosis and polychromasia. Platelets very scarce.

Platelets very scarce.

Platelet Count (3/26): 18,700.

Tourniquet Test (4/16): Negative.

Clot Retraction (4/16): None in 24 hours.

Clotting Time (3/25): 7.5 minutes. Bleeding time: 16.5 minutes.

Cholesterol (3/23): 147 mg. per cent.

Icterus Index (3/23): 6.

Nonprotein Nitrogen (3/23): 92, (3/25): 75, (3/28): 55, (4/3): 40, (4/17): 41.

Total Serum Protein (3/26): 6.03; albumen, 3.86; globulin, 2.17.

Serum Calcium (3/25): 10.0 mg. per cent; serum phosphorus, 4.6 mg. per cent.

Fragility Test (3/25): Same as control.

Blood Cultures: 3/22—*Staphylococcus aureus*

3/25—sterile

3/26—*Staphylococcus aureus* 40 col./cc.

3/27—*Staphylococcus aureus*

4/1 —sterile

4/3 —sterile

4/8 —sterile

4/10—sterile

Agglutinations (3/25): *B. typhosus*—negative; *B. paratyphosus* B—negative; *B. paratyphosus* A—positive 1:20; *B. suis*—negative.

Wassermann (3/29): Positive; (4/1)—negative.

Spinal fluid (3/25): 10 WBC; protein 38 mg. per cent; Wass. negative; mastic curve—0 0.

Fishberg (3/26): 1.016, 1.016, 1.018.

Phenolsulfonphthalein (3/25): 37 per cent excretion in two hours.

Stools: 12 specimens examined, 8 contained blood and were guaiac positive. Rhabditiform *Strongyloides stercoralis* were found in five specimens.

Gastric Analysis: 7 cc. free HCl after histamine.

X-ray of Chest (3/22): Numerous old fractured ribs. Heart a little large. Marked dilatation of aorta, mostly on the right where there is an aneurysm. Considerable calcification in aortic wall.

3/26: Marked hypertrophic arthritis of spine. No suspicious shadows in kidneys, ureters or bladder.

Gastro-intestinal Series (3/29): No upper gastro-intestinal lesion.

Bone Marrow Biopsy: Marrow appears hypoplastic.

**Course:** During the hospital period he ran a grossly irregular spiking fever which at times reached 106° and at other times remained around 99° for several days. Showers of petechiae were noted several times. He had shaking chills at irregular intervals. He complained of dysuria and incontinence which improved after cystoscopy. It was repeatedly stated that the murmurs did not change. No mention is made of the fingers. The spleen became palpable after several weeks in the hospital. At times he complained of lightening pains in the knees and legs. He developed a small cutaneous abscess on the left knee which was drained and healed. Later he developed frank purpura and had several episodes of epistaxis. He ran a persistent leukopenia and thrombocytopenia.

He received 15 transfusions of whole blood with a temporary rise in hemoglobin and red cell count. Five cc. liver extract was given daily from 3/27 to 4/3 then at intervals of two or three days until 4/17. During this time the reticulocyte count never exceeded 0.8 per cent. Sulfanilamide 0.8 Gm. every four hrs. was started on 3/27 but was discontinued on the following day because of a WBC of 900. He was then given several injections of pentnucleotide without specific effect. He was then put back on sulfanilamide for a short time. On 3/30 sulfamethylthiazole was started and was continued until 4/10 with no specific effect on the fever. There was a relative bradycardia (pulse 60–70) throughout most of the course until the last week when he developed a tachycardia. During the last week the temperature remained high around 104° to 106°. There was profuse sweating. He grew progressively weaker and at times was stuporous but rational at other times. The blood pressure was well maintained until the last day when it fell to 80/40. He became incontinent of urine and feces. Potassium iodide 25 drops three times daily had no effect during the last two weeks. He was again given sulfamethylthiazole during the last three days without effect. He went progressively downhill and died on April 23.

It has been felt that a lag of two or three months between the appearance of the quiz case and the publication of its answer is inconvenient. Therefore, starting with this issue, we shall print the answer to each month's case on another page of that same issue. For the answers to all the cases which have appeared so far, please turn to page 512.

*If the management of the minor psychoses, psychosomatic disorders and perhaps the early stages of the major psychoses is to be handled effectively, psychiatry and psychiatric procedures must pervade the other clinical fields. One of the ways in which this can be done is described by the author. In view of the changing pattern of hospital practice with the broadening of hospital pay plans, this procedure may find an increasing place in private practice as well as in teaching and clinic services.*

## The Role of a Psychiatrist in a General Hospital\*

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As you will notice, my paper has to do with the role of a psychiatrist in a general hospital and not the value of a psychiatric service to a general hospital. This latter topic has been well discussed in the past. There is nothing I could add to what has been pointed out. However, I have worked in a general hospital for the past five years handling consultations from the medical and surgical wards and I have formed a few ideas as to what my job should be. I have had no service of my own and have had no ward where my cases were placed. I saw the cases on consultation, but actually it has worked out that no departmental considerations ever came up. I simply was available to any department that asked for my services and, while seeing the case, was to all intents and purposes a member of that department.

This type of work is different from running a psychiatric ward in a general hospital. It is different in many ways. Of course, I am asked to see a good many cases that are routine psychiatric disorders, such as a few of the functional psychoses that always slip by a general hospital admission office, the seniles, and the toxics. The most important part of my work, though, is not with these people but with the cases who were admitted because they were diagnosed as having the common physical disorders such as peptic ulcer, migraine, cholecystitis, thyrotoxicosis, heart disease, etc. These people are in the hospital because of physical diagnoses and not because of any suspected emotional trouble. They are referred to the Psychiatric Liaison Department when their physical status is found to be normal or when the internist feels that he has detected a psychiatric element.

If I find that an emotional factor is accounting wholly or in part for the patient's complaints I undertake treatment. The patient stays where he is. The same interns and residents see him and he stays on

the same service. I am simply added to the situation and the patient never feels that he has been discarded or that his care has undergone any particular change. If patients inquire about my status or ask if I am from "Psycho" I can truthfully tell them, "No." I can tell them that I work and have my office in the General Hospital but I am a specialist in helping people with emotional disorders. Rarely, however, am I asked about my status.

This arrangement works very smoothly. Patients have no objection to the system, and I rarely encounter that initial resistance to seeing a psychiatrist. The Psychiatric Liaison Department is an accepted part of the General Hospital even though it is of the Department of Psychiatry. Because of this the doctors talk to me as though I have nothing to do with the Psychopathic Hospital, and I have learned a great many revealing things about myself. We all talk about the gulf that exists between psychiatry and the other specialties, but I am afraid not many psychiatrists realize just how wide it is and how little we as psychiatrists are doing to close it. My point here is that the psychiatrist's main role in the general hospital is to bring psychiatry into a better relationship and to develop psychiatric understanding in the men who work on the medical and surgical wards. If psychiatrists don't give them such an understanding, who can?

Psychiatrists can talk and can publish articles but no one pays much attention. Internists are a realistic group of people and they pay off on results. Psychiatrists can produce results in the general hospital if they will only make themselves available and identify themselves with the general hospital. Quite often I am called in to see a case that has been a diagnostic problem for four or six weeks. The case will be an anxiety state, perhaps, and may show marked improvement almost immediately. I have been able to discharge such cases symptom free after two or three visits. Incidents such as these get attention. The internists come around and they want to know.

\* From the Psychiatric Liaison Department, Colorado General Hospital, Denver, Colo.

Presented to the Central Neuropsychiatric Association, Denver, Colo., October 5, 1946.

They do not like to make mistakes any more than psychiatrists do, but they object to us sitting in our psychopathic units telling them of their mistakes. When they are shown results they pay attention. They won't see the results if these cases are transferred from the general hospital wards.

If a patient must be transferred to a psychiatric unit to receive treatment for a minor anxiety or hysteria, the referring service is going to be sure that no organic factors were overlooked before the transfer is made. This means many laboratory and x-ray procedures. This means a lot of probing for physical symptoms. Psychiatrists know this *only tends to fix a neurosis more firmly than ever*, and deplore unnecessary physical investigation and treatment. Yet what delight they take in finding organic pathology the internist overlooked. And what delight the internist has when he can find organic pathology in a case the psychiatrist has been treating for a neurosis. This intensifies the old "either-or" concept and leads us farther away than ever from the concept of the person as a whole.

The psychiatrist in the general hospital must work as a member of a team. He must be identified with the medical and surgical services so that he sees the cases on the wards as they are being worked up. If he is a member of the team the internist doesn't feel it necessary to rule out every possible chance of organic pathology before the psychiatrist is called in. It is a mutual aid affair, and this is as it should be.

If psychiatrists are in a separate department, even in the general hospital, these late referrals will be the rule. Psychiatrists should not hold themselves apart until an obviously maladjusted person is sent as to a court of last appeal. When the patient is transferred to a psychiatric service he usually views it as a departure from regular medical care and then it is necessary to overcome a lot of resistance. Also a lot of people who could be helped will go home and probably go home angry. And if the psychiatrist is not a part of the general medical team a lot of cases with emotional components to their illnesses will never be referred to him. He must be on the spot to help the internist recognize these cases. He won't be wanted there, though, unless he produces results that make him welcome. The psychiatrist in the general hospital should actually feel that he belongs to the department of medicine or surgery or pediatrics as the case may be.

If a separate service exists for the care of these psychosomatic cases other little annoying factors develop. Nurses in a general hospital ward get the idea that a patient on the psychiatric service is not

sick. He is a "psycho" to them and he will get poor care and understanding. Patients learn this distinction and in our present state of public enlightenment the patients on each ward will be alert to see who gets transferred to the psychiatrist. If I am right that the psychosomatic cases should be treated on the general hospital wards then there should be no change from the medical or surgical services. Those cases of a more pure psychiatric nature should be transferred for they need the special care and understanding that only a psychiatric ward can give.

Psychosomatic medicine is a relatively new field. I think that one needs special training in it before he can do a good job. If we have a psychiatrist in a general hospital and one that is familiar with the work, he has another great role—that of doing graduate teaching. All physicians taking training in psychiatry should spend a period of time in the general hospital working with psychosomatics. Since this last war psychiatry has received a tremendous impetus and the general reading public has been led to expect a lot from us. Particularly is the public becoming more and more interested in the fact that psychiatrists see people who do not need institutionalization.

If we profess an interest in psychosomatic medicine, we must be prepared to handle it. Recently a group of internists of the American College of Physicians was taking a course in psychosomatic medicine. They presented a complaint that I am going to pass on and one that I consider a severe criticism of psychiatry. These men were interested in psychosomatic disease to the degree that they took a special course in it. Their interest came from our current literature and from their military experiences. They could recognize the part emotions were playing in some of their patients and were making referrals to psychiatrists. But, their patients, they said, were returning to them after one visit to the psychiatrist. They came back angry, feeling insulted and convinced that the psychiatrist had nothing to offer them and that the doctors had shown an error in judgment. What is wrong?

Let us consider this situation. First, the patients these men are referring are not psychotic, often they do not present the usual picture of a neurosis, and they may be physically well, yet these are the patients who originally went to their doctors with physical complaints, body aches and pains. It has never occurred to them that they do not have some physical abnormality to account for their symptoms. They have never considered emotional conflicts as a possibility, and usually resent any such implication. In other words, their bodies send them to a doctor, not

their worries. They do not consider themselves neurotic and usually no one else has either. Usually they are respected working members of their community and the idea of them needing a psychiatrist is startling and laughable. However, this is just the kind of case psychiatric literature is telling internists that the psychiatrists are prepared to handle. Now, what is wrong? Why can't these people with somatic symptoms of anxiety and tension get the kind of care the internist expects them to have?

Two main explanations are possible. First, the internist may have misled his patient as to what the psychiatrist was going to do, or made a bad referral in some other way. If this is the case, then it is up to the psychiatrist to teach the internist how to refer a patient and what patients to refer. We err if we simply chide the internists or complain. Who besides psychiatrists can teach them? However, if the internist has sold his patient well enough that he keeps the appointment with the psychiatrist, then I am inclined to believe the fault is with the latter if things go badly. I know this second explanation for patients returning to the internist with disgust is true in many instances. Now all psychiatrists have had patients so sick that we could not establish rapport, but they are not the cases who voluntarily keep an appointment with a psychiatrist and they certainly are not the type of case to which I refer when I speak of psychosomatic cases. The internist has no real problem in referring a psychotic person for in those cases the relatives are usually involved and there is no question about the presence of mental trouble. In the case of the patients we are now considering, an entirely different technic is necessary.

The psychiatrist who has dealt almost exclusively with severely neurotic and psychotic people will make mistakes and will proceed along lines that the patient finds most annoying. These patients want an explanation for their aches and pains and they want a logical explanation. They rightfully resent being looked upon as being crazy. They need to feel that the psychiatrist has an interest in their physical well-being and is prepared to look after it. The psychiatrist must be able to consider the somatic complaints as the presenting complaints and make the patient

feel confident that the elimination of the ache or pain is the prime objective. A too obvious approach to a mental status will send the patient back to his doctor complaining that he wanted help for his abdominal pain, not a sanity test. So, I feel the psychiatrist of today must familiarize himself with this type of practice and fulfill the role the public seems to have given him, and, I might add, for which he asked.

If psychiatrists frequent the wards of the general hospital they will appreciate the problems met there much more clearly and, what is more important, patients and doctors get accustomed to seeing them around. A few years ago when I would appear on a medical ward, interns and nurses alike would have jokes and remarks to make about my being out of place. Now my presence is taken for granted and usually I am asked to see cases other than the one I intended to see. This is where we can do our teaching. This is where psychiatrists can meet the other specialties on a common ground and where they can gain mutual understanding and respect. Only by making themselves available, and by being interested in the medical and surgical wards, will those wards ever see any reason to keep and treat a neurotic patient. Only by teaching psychiatric technics right in the general hospital can the psychiatrist put a stop to late referrals and distaste for neurotic patients. By showing the general hospital that these people can be treated while on the medical service, we can create a place for the care of neurotic and psychosomatic cases and avoid having to send them to psychopathic units or discharging them without help.

So, for the next few years at least, I believe the psychiatrist in a general hospital is needed mostly as a teacher and as a person who can disseminate psychiatric thinking among the men of the other specialties. We have taught the internists that many body complaints are based in emotional conflicts. Unless we are prepared to care for the patients with somatic symptoms of anxiety and unless we can show positive therapeutic results in the psychosomatic cases, the internist will see little reason to include us in the care of the patient in the general hospital, and with both the internists and the public we will have enhanced our reputation for being long winded.

# CASE REPORT

## Simple Cyst of the Kidney: Report of Case Illustrating Difficulties of Diagnosis and Successful Treatment by Conservative Surgery\*

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J. S., a 54-year-old white male, was admitted to the Outpatient Clinic of the Department of Urology (James Buchanan Brady Foundation) of the New York Hospital on October 10, 1946 for the relief of dull pain in the left kidney region and lower part of the back.

Seven years before, he had had an attack of sharp pain in the left kidney region, accompanied by blood in the urine, both the pain and hematuria lasting for 24 hours. He remained well for two years, then had a similar attack of pain, of one-half hour's duration, but without hematuria. For the past three years there had been inconstant dull pain in the left kidney area and lower back. There had at no time been pain in the region of the right kidney, and he had no urinary disturbances and no repetition of the hematuria.

Examination in the clinic showed slight enlargement and congestion of the prostate gland, normal prostatic secretion save for a few white blood cells, and clear urine.

Retrograde pyelograms were made on October 26th. In the plain film the right kidney was seen to be larger than the left, with its superior and lateral margins confused by an overlapping soft-tissue shadow which, it was thought, might be the gallbladder. The left pyelo-ureterogram was normal. The right showed the pelvis and calyces to be larger than on the left side, with a questionable filling-defect of the lower calyx. The impression was of a normal left upper urinary tract and minimal hydronephrosis on the right side. However, because the abnormal outline of the right kidney was not satisfactorily explained, and even though no definite indication of tumor existed, better visualization of the kidney outline was deemed advisable.

Excretory urograms were accordingly made two weeks later. These showed a normal left kidney, obscuring of the upper pole of the right kidney by an

overlying soft-tissue mass, and a possible space-filling lesion in the right kidney as indicated by slight distortion of the middle group of calyces. The function of both kidneys was good. A gallbladder series proved the gallbladder to be negative.

Repetition of the retrograde pyelograms, and comparison with the first films, on January 11, 1947, greatly strengthened the impression of a tumor or cyst of the right kidney, and the patient was advised to enter the hospital for exploration of the kidney. At this time his only complaint was of occasional slight pain in the lower back.

He was admitted to the hospital on January 20th. Physical examination at this time showed a well-developed and well-nourished man who did not appear to be acutely ill. His blood pressure was 150/92. The lower pole of each kidney was palpable on deep inspiration, but there was no tenderness in either kidney region and no masses. The physical examination was otherwise essentially negative. The laboratory findings, both as to urine and blood, were within normal limits.

**Operation.** The day after admission, under spinal anesthesia, the right kidney was exposed and delivered through the usual lumbar incision. Examination disclosed a large cystic mass located in the midportion of the dorsum of the kidney. This mass was incised and fluid collected for culture. The free portion of the cystic wall was then resected. While examining the remaining portion of the wall, fluctuation was noted. This was at first believed to be caused by urine in the kidney pelvis. However, careful aspiration of this fluctuant area withdrew fluid similar to that from the resected cyst.

Accordingly, an incision was made in this area, opening up a second, smaller cyst below the first, in the interior of the kidney. The intervening cystic wall was completely resected, converting the two cavities into one. The remainder of the cystic wall was then treated with carbolic acid (95 per cent) followed by alcohol (70 per cent). The residual cavity was

\* From the Department of Urology (James Buchanan Brady Foundation) of the New York Hospital.

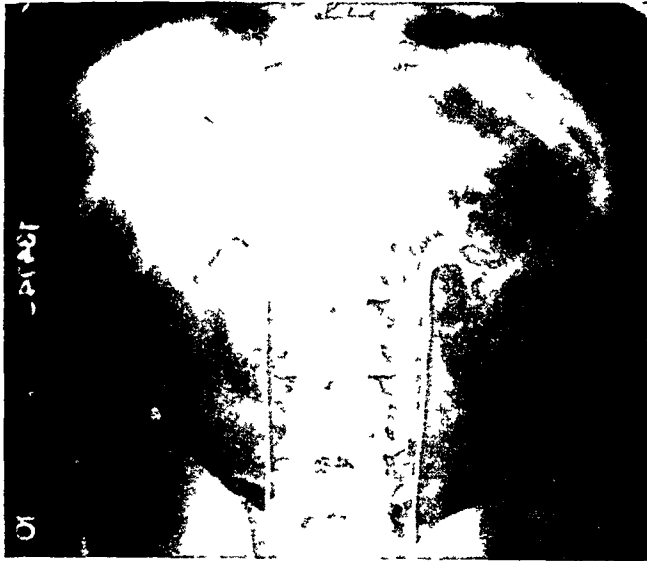


FIG 1. Pre operative retrograde pyelogram showing irregularity of right kidney outline in midportion of dorsal surface, and distortion of middle group of calyces. Left kidney normal.

packed with fat, and the edges of the kidney were approximated over it with three mattress sutures of chromic ribbon gut placed through the kidney capsule.

The kidney was returned to its fossa and fixed in position by a Deming nephropexy. A Penrose drain was left in the perirenal space, and the kidney wound was closed in layers in the usual manner.

Postoperatively the patient did very well. The wound healed promptly and he was discharged home on the eighth postoperative day, to be followed in the clinic. An excretory urogram made on the day before his discharge showed a normal right urogram, without distortion.

The patient returned to the clinic several weeks later for checkup, at which time he was entirely asymptomatic.

**Laboratory Report.** The report of the pathologist was as follows:

**Gross Examination of Specimen**—The first specimen consists of a 4 cm.-across circular mass of cystic tissue which contains within itself multiple small cysts which contain clear fluid. The cyst measures about 1/5 cm. in diameter. With the specimen is a second portion which appears to be part of normal kidney which was attached to the cyst wall.

**Microscopic Examination.**—The wall of this cyst shows that it is a degenerated structure in which there are remnants of renal tissue scattered through a dense scar like the band of connective tissue. At one point the cyst is multiloculated, some of the loculi being larger than a 16 mm. field and filled with light coagulum. The renal tissue is composed of fibrotic glomerular masses of tubules re-



FIG 2. Pre operative excretory urogram showing distortion of right kidney outline by mass

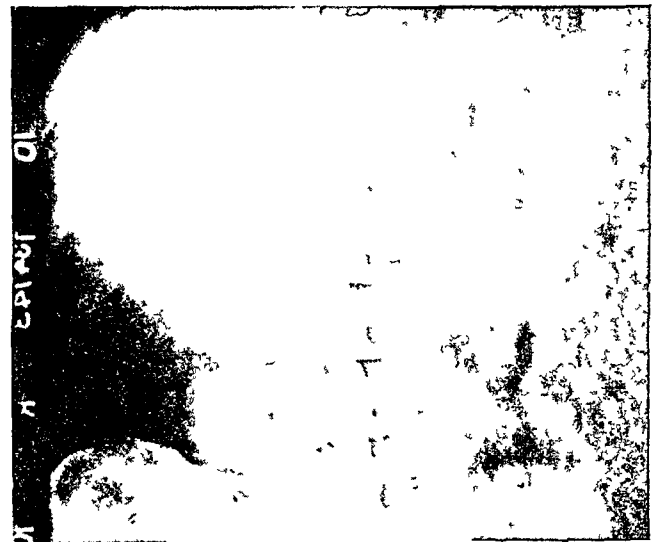


FIG 3. Excretory urogram, seventh postoperative day. Right kidney normal in outline, no distortion of calyceal system.

sembling thyroid acini and filled with a material quite similar to colloid. The picture is that of a degenerated cyst possibly associated with a focal pyelonephritis of the chronic type. The kidney attached to the cyst is more normal in appearance although it is extremely fibrotic. Some of its tubules contain brown casts apparently representing old blood as corpuscles can be made out in some of them.

**Diagnosis**—Degenerated cyst of kidney probably secondary to focal chronic pyelonephritis

### COMMENT

1. Although simple cysts of the kidney usually occur singly, it is not uncommon to find two or more in the same kidney, as in this case; therefore, the term "solitary renal cyst," used to describe this lesion, is a misnomer.

2. Such cysts occur most frequently at either pole of the kidney, but they may arise in the midportion, or on the anterior, posterior, lateral, or medial surface. In the case described here, one cyst was located in the midportion of the dorsum and a second, smaller cyst was found just below the first, deep in the interior of the kidney, where it caused pressure on the middle and lower calyces, giving the slight distortion observed in the pyelograms.

3. The symptomatology varies and is often confusing. In cysts of large size, pain in the kidney region of the affected side, due to pressure of the cyst, is common, and urinary symptoms are present in the majority of cases. Some renal cysts cause pressure on intra-abdominal organs and produce symptoms simulating those of cholecystitis or peptic ulcer. A large cyst at the upper pole may cause pressure on the diaphragm, producing cough, dyspnea, and pain referred to the shoulder.

The only symptoms in this case were an attack of sharp pain in the left kidney area, with hematuria, seven years earlier; a second attack of similar pain two years later, and, for the last three years, incessant dull pain in the left kidney region and lower part of the back. There were no urinary symptoms, and at no time was there pain in the region of the right kidney. Hematuria, while a prominent and very important symptom in malignant tumor of the kidney, is not of frequent occurrence in simple renal cyst. Retrograde and excretory pyelograms showed a normal urinary tract on the left side and findings indicative of a mass in the kidney on the right (painless) side.

4. Both retrograde and excretory pyelograms are very helpful in revealing the presence of a kidney tumor. However, it is not possible to state definitely

from the x-rays whether a tumor of the kidney is a cyst or a malignant growth. Surgical exposure and exploration of the kidney should be done, for if the tumor is a cyst, it should be removed to prevent progressive destruction, and eventual loss, of the kidney; and if it is a malignant growth, only prompt removal of the kidney will save the patient's life.

5. Since most simple renal cysts tend to grow out from, rather than into, the kidney substance, involvement of the kidney parenchyma is usually minimal—the destruction of kidney tissue by compression occurring only in the area adjacent to the cyst. For this reason, the function of kidneys containing simple cysts will usually be found to be within normal limits unless they have been affected by hydronephrosis due to compression or distortion of the kidney pelvis or ureter. Cysts in the interior of the kidney, such as the smaller one described here, are more likely, as they grow, to cause compression or distortion of the kidney pelvis or ureter.

6. Because the function of the affected kidney is usually good, conservative surgery, rather than nephrectomy, is indicated in most cases. We have performed the operation described here—namely, resection of the free portion of the cyst, phenolization of the remainder of the cystic wall, packing of the residual cavity with fat, and repair of the kidney with ribbon gut\*—numerous times, with excellent results. In this case, the patient was able to leave the hospital on the eighth postoperative day, at which time an excretory urogram showed a normal-appearing kidney without distortion. On his return to the clinic for a checkup, two weeks later, the patient was entirely asymptomatic.

\* Lowsley, O. S., and Mark S. Curtis: The surgical aspects of cystic disease of the kidney, *J. A. M. A.*, 127:1112 (April 28) 1945.

### Answers to WHAT'S YOUR DIAGNOSIS?

December—Disseminated lupus erythematosus.

January—Subacute yellow atrophy.

February—Amyloid disease.

March—Multiple pulmonary emboli originating from thrombophlebitis of the pelvic veins. Right heart failure.

April—Pernicious anemia.

May—Bacteremia due to *Staphylococcus aureus*; syphilitic aortitis with aneurysm; tabes dorsalis.

# Clinicopathologic Conference

I. A. BIGGER, M.D. and F. L. APPERLY, M.D.

DEPARTMENT OF SURGERY

DEPARTMENT OF PATHOLOGY

MEDICAL COLLEGE OF VIRGINIA

RICHMOND, VIRGINIA

## CASE RECORD

The patient, a 13-year-old colored male, was admitted to the hospital acutely ill. About three weeks before admission he had had an "open sore" on his right foot. About ten days before admission his right ankle became painful. Shortly after that he developed pain in his right hip and, then, in his left ankle. The pains were severe enough to confine him to bed. Five days before admission the patient began to be short of breath, and was conscious of rapid heart action. Associated with this were fever and three or four hard chills. He had received sulfathiazole for several days prior to admission.

Physical examination revealed a young colored male acutely ill, with rapid shallow respiration and evidence of dehydration. T. 103; P. 145; R. 40; B.P. 130/75. The sclerae appeared slightly icteric. The mucous membranes were pale. There were several aphthous ulcers in the mouth. Medium moist râles were heard over the chest posteriorly. The point of maximum aortic impulse was 8 cm. from the mid-sternal line in the fourth left intercostal space. The heart sounds were of poor quality. There were no murmurs. The abdomen was negative. Both ankle joint, both knee joints and the right hip joint were tender, warm and swollen. There was limitation of motion at these joints due to pain.

Blood work on admission: red blood cells 3,100,000; hemoglobin 44 per cent; white blood cells 18,900 with 88 per cent polymorphonuclears. Urine showed a specific gravity of 1.016; 2 plus albumin and 3 to 4 white blood cells per high power field. A chest x-ray on admission showed mottling throughout the left lung, and the lower half of the right lung. There were several small cavities in the upper portions of both lungs, and in the lower right lung. Among further blood studies were: nonprotein nitrogen 42 mg.; sulfathiazole level (24 hr. after admission) trace; reticulocytes 1 per cent; wet smear "few sickle cells"; icteric index (two

days after admission) 18, repeated two days later, 7. Several sputum examinations were negative for acid-fast bacilli.

Two days after admission the right knee joint was aspirated, and 20 cc. of yellow turbid fluid with a cell count of 1,050, majority polys, was obtained. On that day a pericardial friction rub was noted. The patient was placed on salicylates. Fever declined, but respirations and pulse rate remained elevated. The joint pains continued to be severe. Next day aspiration of the left ankle joint revealed thick pus. Four days after admission fluctuation was noted over almost the full length of the left tibia. This area was incised and a "great deal of pus gushed forth." Five days after admission the temperature rose to 102° (salicylates discontinued). The neck veins were full. There was some widening of cardiac dullness in the region of the left auricle. The pericardial friction rub had disappeared; no murmurs were heard. The lungs were filled with many moist râles. The blood pressure was 110/40. About one hour following this examination the patient died.

## DISCUSSION

DR. I. A. BIGGER: I want to point out what seem to me to be the significant points in this clinical record. There are a good many things we would like to know, but cannot find out as Dr. Apperly tells me the record has disappeared from the record room. This boy's age is probably of no significance in so far as the differential diagnosis is concerned. Both conditions which I have in mind would fit in well in this age group.

As you know, this boy had an open sore on his right foot some three weeks before he was admitted to the St. Philip Hospital. About ten days before admission to the hospital, or somewhere between one and two weeks after the development of this sore on his foot, he developed swelling, soreness and pain in his right



ankle joint. The fact that the joint involved was on the same side as his original infection may be significant. Shortly after this he developed pain in his right hip and then in his left ankle; pain severe enough to confine him to bed. About five days before admission to the hospital he developed shortness of breath and was aware that his heart's action was quite rapid. He had considerable fever and several severe chills. When admitted to the hospital he was obviously quite sick, appeared to be dehydrated, his temperature was 103°, pulse rate 145, respirations 40 per minute and his blood pressure was 130/75. He was obviously anemic and appeared slightly icteric; there was evidence of infection in both lungs. The point of maximum impulse of the heart was 8 cm. from the mid-sternal line. The heart sounds were of poor quality, no murmurs were heard. Examination of the abdomen was described as negative. Both ankle joints, both knee joints and the right hip joint were tender and swollen.

Examination of the blood showed a high leukocyte count, 18,900 with 88 per cent polymorphonuclear leukocytes, marked secondary anemia with 3,100,000 red blood cells and 44 per cent hemoglobin. The NPN was elevated, 42 mg. His icteric index two days after admission was 18, a slight elevation, but two days later was 7. The urine showed nothing of especial significance, there was albumen 2 plus, and 3 to 4 white blood cells per high power field. A roentgenogram of the chest showed mottling throughout the left lung and through the lower half of the right lung. The statement in regard to the chest findings is unclear in that it first says there was mottling throughout the left lung and lower half of the right lung and then says there were cavities in the upper portions of both lungs. I presume the term mottling was used to indicate areas of increased density, without evidence of cavity formation in the lower half of the right lung and throughout the left lung. In addition to this, I take it, there were shadows characteristic of cavitation in the upper portions of both lungs. The sputum unfortunately is reported only in so far as acid-fast organisms are concerned, none was found. About two days after admission the right knee joint was aspirated and 20 cc. of yellow turbid fluid was removed. This showed more than 1,000 cells per cubic centimeter, the majority of them polymorphonuclear leukocytes. On that same day, the second day after admission, it was noted he had a pericardial friction rub. Salicylates were administered apparently without any particular benefit, though his fever did subside. The next day, that is the third day after admission, the left ankle joint was aspirated and thick

pus was obtained. Four days after admission it was noted that he had fluctuation over his left tibia and when this was incised a large quantity of pus was evacuated. The following day his temperature rose to 102°. On the same day the neck veins were observed to be distended. The area of cardiac dullness was found to be increased and the pericardial friction rub was no longer heard. The friction rub was present for only three days. No murmurs were heard over the cardiac area. Numerous moist râles were heard over both lungs. It is stated that his blood pressure at this time was 110/40 which is very confusing. I have no idea how to explain the wide pulse pressure in the presence of cardiac tamponade. One would expect a low pulse pressure.

As I see it, the significant points in this boy's story are the open sore on his right foot followed by infection in the right ankle joint. He then developed involvement of several joints including the knee joint, the other ankle joint and the hip joint. The occurrence of dyspnea is of no significance in so far as the differential diagnosis is concerned. The x-ray findings in the lungs are very significant. I believe this is one of the most important findings in so far as the differential diagnosis is concerned. The type of fluid obtained from the ankle joint is significant as it was described as frank pus. The appearance of fluctuation over the tibia is very significant in connection with the differential diagnosis for it suggests bone involvement which of course would not occur in acute rheumatic fever.

The two conditions I would think of first are acute rheumatic fever, or a pyogenic infection with septicemia and pyemia. I take it that acute rheumatic fever was considered as a definite possibility. The distention of the neck veins, widening of the area of pericardial dullness and the presence of a pericardial rub are compatible with this diagnosis, but multiple lung abscesses, osteomyelitis of the tibia and frank pus in the ankle joint could not be explained on the basis of this diagnosis alone. All of these findings are compatible with a pyogenic septicemia, so this seems to be the likely diagnosis. The pyogenic infection of the right foot may have spread directly to the right ankle joint or he may have developed a systemic infection from the original foot infection with accidental involvement of his right ankle joint along with the other joints. In such a septicemia or pyemia, one often finds involvement of many organs. This boy probably had abscesses in many of his organs including his lungs and his myocardium as well as infection in the various joints. A subepicardial abscess evi-

dently ruptured into the pericardial sac giving rise to suppurative or purulent pericarditis.

To summarize, most of the findings in this case would be compatible either with acute rheumatic fever or pyogenic septicemia. As I pointed out, in his age group one might well expect either an acute osteomyelitis with septic arthritis, septicemia and pyemia with involvement of his lungs, heart, pericardium, etc., or acute rheumatic fever. The joint involvement, the fever and chills, the high leukocyte count and the anemia are all compatible with either condition. So are the widened area of cardiac dullness, the full neck veins and the pericardial friction rub. The findings most significant in connection with the differential diagnosis between these conditions are multiple lung abscesses, purulent arthritis and the abscess over the entire extent of the tibia, pointing to acute pyogenic osteomyelitis. These latter conditions are in keeping with septicemia and pyemia but none of them are caused by acute rheumatic fever.

DR. FRANK L. APPERLY: The findings on this case, some of which you already know, were the open sore on the right foot, the swelling of the right ankle, the right hip, and then the left ankle, and the right and left knees. Later on we find some evidence of abscesses in the lungs, and finally there is pus in the left tibia. Although this was described as the last finding in point of time, the pus was large in amount, involving a large part of the tibia. This was an acute suppurative osteomyelitis. Obviously it must have become infected much earlier than the record would indicate. On section of the body the heart showed a pericarditis with 425 cc. of blood-stained fibrinopurulent fluid. That certainly seems an enormous volume of fluid to be contained in the pericardium of a small boy. In addition there were a number of small pinhead abscesses beneath the epicardium on the posterior surface of the heart, and an old patch of organized fibrous adhesions at the apex. The right lung weighed 530 Gm., the left 480 Gm. and both showed old apical fibroses. In the left apex was an old cavity with fibrous walls, probably an old tuberculous cavity, but I regret to say, it was not microscopied. In the bases of the lungs abscesses and necroses together with a good deal of edema were found. The pleurae each contained 100 to 200 cc. of clear yellow fluid but there was no pleurisy. The spleen was of the type usually described as a splenic "tumor," that is to say it weighed 200 Gm. (the normal for that age being 110 to 120 Gm.), an enlargement of about 50 per cent or so, and was soft, red and mushy. The liver weighed 1,700 Gm. and was swollen, and congested with some central atrophy. The kidneys were likewise swollen

and enlarged about 50 per cent, but there were none of the abscesses in the kidney that we might have expected. Cultures made from the tibial pus in life and from the pericardial fluid after death showed the *Staphylococcus aureus*. So the diagnosis from the autopsy findings were exactly as Dr. Bigger has described, namely, staphylococcus septicemia and pyemia.

What was the order of events? Sometimes in these staphylococcus infections we cannot find the point of primary infection. But in this case I think the history would make it clear enough that the sore on the right foot was the probable point of entry. This organism is a common inhabitant of the skin, sometimes getting in through a small abrasion, but sometimes we cannot find the entry point. Sometimes by the time the patient dies the original point of entry has closed up or healed and there is no evidence of it at all.

From the right foot the infection appears to ascend to the ankle, the hip and then affects the left leg. Abscesses in the lung in this case would almost certainly arise from septic emboli, most probably from the large veins involved in the acute osteomyelitis of the left tibia. But you will notice here that if we take things as they were discovered in the record, the tibia came rather later in the story. On the other hand it seems a little curious that on the fifth day, when it was discovered, the pus was already present along most of the length of the bone, and the osteomyelitis must therefore have been going on for a fairly long time, so I am inclined to disregard the timing of events in the records, and to believe that the osteomyelitis occurred rather early in the game. Of course I cannot say when, but I shall make this assumption. We know that in small boys with a bacteremia, a physical injury is liable to precipitate an infection at the site of trauma. Now small boys are always knocking their shins or getting kicked, or putting some undue strain on their tibiae. At any rate youngsters of this age are those most likely to get an acute osteomyelitis. I am inclined to put that fairly early in the story. It fits in with the history too. And from the osteomyelitis there arose septic emboli, which, travelling up the inferior vena cava gave rise to the lung abscesses, which in their turn led to blood-borne infection, abscesses of myocardium and fibrinopurulent pericarditis. The question raised by Dr. Bigger about the large pulse pressure in the presence of pericardial fluid is disturbing. On the findings here I don't know any way in which we can explain these, unless perhaps by assuming that the inflamed pericardial sac stretched just as fast as the purulent

fluid accumulated, in which case no tamponade effect (diminished cardiac inflow and low pulse pressure) would be present. Of course we always have to keep in mind that the pulse pressure as seen in the arm is not necessarily the same as the pulse pressure as seen in the viscera. In fact we published evidence some time ago that the two probably vary inversely, but I will not go into that now.

I will remind you again that the *Staphylococcus aureus* is an organism which is commonly found on the skin, but usually does not give rise to anything but localized infections, such as boils, carbuncles, etc.

Sometimes, however, it will get into the tissues, and may then break away from the usual localizing influences and even give rise to septicemia. In that case it is a pretty dangerous condition, because about 80 to 85 per cent of these patients will die with abscesses distributed pretty much as we have seen them here in the myocardium and lungs, and usually in the kidneys as well.

DR. BIGGER: Was there any endocardial involvement?

DR. APPERLY: No, there was no endocardial involvement.

### Beaumont's Description of the Gastric Juice

Pure gastric juice, when taken directly out of the stomach of a healthy adult, unmixed with any other fluid, save a portion of the mucus of the stomach with which it is most commonly, and perhaps always combined, is a clear, transparent fluid; inodorous; a little saltish; and very perceptibly acid. Its taste, when applied to the tongue, is similar to thin mucilaginous water, slightly acidulated with muriatic acid. It is readily diffusible in water, wine or spirits; slightly effervesces with alkalis; and is an effectual solvent of the *materia alimentaria*. It possesses the property of coagulating albumen, in an eminent degree; is powerfully antiseptic, checking the putrefaction of meat; and effectually restorative of healthy action, when applied to old, foetid sores, and foul ulcerating surfaces.

Saliva and mucus are sometimes abundantly mixed with the gastric juice. The mucus may be separated, by filtering the mixture through fine linen or muslin cambric. The gastric juice, and part of the saliva will pass through, while the mucus, and spumous or frothy part of the saliva, remains on the filter. When not separated by the filter, the mucus gives a ropiness to the fluid, that does not belong to the gastric juice, and soon falls to the bottom, in loose, white flocculi. Saliva imparts to the gastric juice, an azure tinge, and frothy appearance; and, when in large proportion, renders it foetid in a few days; whereas the *pure* gas-

tric juice will keep for many months, without becoming foetid.

The gastric juice does not accumulate in the cavity of the stomach, until alimentary matter be received, and excite its vessels to discharge their contents, for the immediate purpose of digestion. It then begins to exude from its proper vessels, and increases in proportion to the quantity of aliment *naturally* required, and received. A definite proportion of aliment, only, can be perfectly digested in a given quantity of the fluid. From experiments on artificial digestion, it appears that the proportion of juice to the ingesta, is greater than is generally supposed. Its action on food is indicative of its chemical character. Like other chemical agents, it *decomposes*, or *dissolves*, and combines with, a fixed and definite quantity of matter, when its action ceases. When the juice becomes *saturated*, it refuses to dissolve more; and, if an excess of food have been taken, the residue remains in the stomach, or passes into the bowels, in a crude state, and frequently becomes a source of nervous irritation, pain and disease, for a long time; or until the *vis medicatrix naturae* restores the vessels of this viscus to their natural and healthy actions—either with or without the aid of medicine.

—From *Experiments and Observations on Gastric Juice and the Physiology of Digestion*, 1833, pp. 84-86.

## Trends in Immunization of Children\*

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Present practice in immunization of children includes active immunization against diphtheria, whooping cough and smallpox, with coincidental protection against tetanus in many instances. Passive protection against measles, whooping cough and infectious hepatitis is available, in addition to the classical prophylactic use of diphtheria antitoxin under certain conditions of exposure to that disease. With the exception of chemotherapy and antibiotic therapy, no field of medical research is receiving more attention than that of active and passive protection against communicable disease. Before reviewing newer work in this field, present day practices should be considered. The following Table represents approximately the recommendations of the committee on immunization procedures of the American Academy of Pediatrics. It will be noted that with the exception of smallpox vaccination, all active immunization are withheld until after six months of age.

TABLE 1

AGE	IMMUNIZATION	REMARKS
3-12 mo.	Smallpox Vaccination	Repeat at 6 and 12 years or during an epidemic.
9-12 mo.	Diphtheria Toxoid	Schick test or booster injection at 18-24 months. Repeat Schick or booster at 6 and 12 years.
6-9 mo.	Whooping Cough Vaccine	Question of the need for vaccination after 6 years.
3rd year	Tetanus Toxoid	Optional. May be given with diphtheria toxoid.
After 2 years	Typhoid Vaccine	Given only on special indication. Not routine in most communities.

Table 1. Adapted from the recommendations of the Academy of Pediatrics. It is of interest to note that the American Public Health Association in its booklet "The Control of Communicable Diseases" (1945) advises active immunization against whooping cough "not before the third month, and preferably before the sixth month."

\* From the Department of Pediatrics and Communicable Diseases, University of Michigan Medical School, Ann Arbor, Mich.

Is there any valid reason for changing this schedule either in regard to timing or the selection of antigens? It must be admitted that as far as diphtheria and smallpox are concerned the timing suggested by the Academy of Pediatrics is entirely adequate. Experience has shown that smallpox vaccine and alum-precipitated diphtheria toxoid have been very effective antigens. A study of whooping cough mortality shows (Table 2), however, the inadequacy of present practices with respect to immunization against whooping cough and certainly favors earlier immunization as recommended in the A. P. H. A. booklet.

TABLE 2

*Deaths from Pertussis in the U. S. 1938-1940*  
(U. S. Census Bureau mortality statistics)

AGE	NUMBER	PERCENT-AGE	CUMULATED %
1 mo.	396	3.7	—
1 mo.	1166	10.9	14.6
2 mos.	1061	9.9	24.5
3 "	791	7.4	31.9
4 "	646	6.0	57.9
5 "	515	4.8	42.7
6 "	502	4.7	47.4
7 "	458	4.3	57.7
8 "	447	4.2	55.9
9 "	417	3.9	59.8
10 "	361	3.4	63.2
11 "	363	3.4	66.6
12 "	2104	19.6	86.2
2 yrs.	668	6.2	92.4
3 yrs.+	828	8.8	100.2
10,723			

When whooping cough vaccination is delayed until the seventh month, it can be readily perceived that by the time the child has developed immunity (which, according to Dr. L. W. Sauer, is two to three months after the immunization has been completed) fully two-thirds of whooping cough mortality has been realized. Every month that whooping cough immunization can be advanced should see a lessening of deaths from this disease. As a matter of fact, with our present practice

of not starting this immunization until the sixth or seventh month, it seems unlikely that as many lives are being saved as we might think, but rather that a great many children are escaping an attack of the disease which in all probability would not have been fatal. A study of deaths from whooping cough by years shows a downward trend from 1930-1943. In addition to crediting whooping cough vaccinations with preventing epidemics of the disease and therefore sharply reducing the number of very young infants who contract it, it seems almost certain that sulfonamides have done a great deal to reduce deaths from whooping cough complications.

The inevitable question is, can whooping cough vaccination be given earlier enough to be effective in preventing whooping cough in babies who are under ten months of age, or is the very young infant so poor a producer of antibodies that it is not worthwhile trying to immunize him by injection of good vaccine? Sako has given us the answer to the first of these two questions as Table 3, which is compiled from his data, shows.

TABLE 3

*Early Immunization Against Whooping Cough Using Alum Precipitated Vaccine\**

Sako et al. J. A. M. A. 127:379 (Feb. 17) 1945  
Number of Patients Immunized—3793

	IMMUNIZED		NONIMMUNIZED	
	Negro	White	Negro	White
Number	1642	192	1753	212
Familial Exposures	141	18	135	14
Contracted Whooping C	27	3	118	9
Severe Course	2	0	114	9
Death	0	0	12	1

A study of Sako's results indicates beyond question that he and his associates were able to confer a completely protective immunity on the majority of infants in spite of the fact that vaccination was begun in many instances as early as the first month. These workers were able to do follow-up studies and determine actual exposures, and failures and successes of immunization with a thoroughness which has not been reported elsewhere. In addition, their work was supplemented by laboratory studies of actual antibody titers in the blood serum of 500 of these children. Their results are set forth in Table 4.

\* The immunizing agent was alum-precipitated pertussis vaccine containing 40 billion bacilli per cubic centimeter. It was given according to the following schedule: 0.2 cc. in first or second month of age, 0.3 cc. in second or third month, and 0.5 cc. in third or fourth month.

TABLE 4

*Results of Repeated Rapid Slide Agglutination Tests in 500 Negro Infants in Group A*

AFTER COMPLETION OF IMMUN- IZATION	MÖDER- ATELY POSITIVE (1:160- 1:640)	STRONGLY POSITIVE (1:640- 1:5120)	TOTAL POSITIVE	PERCENT- AGE POSITIVE
1 mo.....	96	201	297	59.4
2 mo.....	145	199	344	68.8
3 mo.....	159	213	372	74.4
4 mo.....	163	215	378	75.6
6 mo.....	158	205	363	72.6
8 mo.....	160	201	361	72.2
10 mo.....	179	184	363	72.6
12 mo.....	165	187	352	70.4
18 mo.....	171	157	328	65.6
24 mo.....	189	126	315	63.0

This proves that as early as the third month three-fourths of their patients showed positive agglutinins in the blood, the majority of them having levels above 1:640 which experience has shown correlates with a high degree of immunity.

The question of antibody formation in infants under six months of age is not definitely settled. It must be admitted that the medical profession was for several years strongly influenced by Sauer's recommendation<sup>1</sup> that whooping cough immunization be withheld until the seventh month. Fox and Knott<sup>2</sup> have pointed out that Sauer's original report, which cited an incidence of whooping cough seven times more frequent in children vaccinated before three months of age as compared to children vaccinated after seven months of age, reveals some interesting facts on further analysis. Of 1,110 infants vaccinated early, 91 contracted whooping cough during the subsequent four years. Thus, one sees that more than 90 per cent of this group was protected for at least a four-year period in spite of the fact that their vaccination occurred before the third month. Changing practice in whooping cough vaccination, therefore, is chiefly toward earlier administration of the immunizing course and perhaps the use of alum-precipitated vaccine either alone or in combination with other antigens, particularly diphtheria and tetanus toxoids.

We cannot leave the discussion of whooping cough until we have mentioned a very important adjunct to the prevention of death in young infants who contract the disease. I refer to the use of hyperimmune anti-pertussis serum of human origin. Some six years ago our attention was first called to the use of hyperimmune human serum in the treatment of whooping cough in young infants by the work of McGuinness

and co-workers<sup>3</sup> at the University of Pennsylvania. They obtained a hyperimmune whooping cough serum by actively immunizing healthy young adults who had had whooping cough in childhood. These adults were given a course of vaccine prepared according to the directions of Dr. L. W. Sauer and in most instances it was possible to develop an antibody titer up to 1:2,560 in these prospective donors. Subsequent reports by McGuinness and others have indicated that this hyperimmune serum may, indeed, be the difference between life and death in the child who contracts whooping cough under six months of age. We have used the McGuinness product which is obtainable from the Philadelphia Serum Exchange of the University of Pennsylvania and also a somewhat more refined preparation of excellent potency, produced by Cutter Laboratories, Berkeley, California, which is sold under the trade name Hypertussis. This product is reduced to the gamma globulin fraction which contains the antibodies and is, therefore, less bulky than unconcentrated serum preparations.

For several years now it has been routine in our isolation hospital to use one or the other of these products at the earliest possible moment in all children under ten months of age who have pertussis. It is usually advisable to repeat the dose (the contents of one vial) on the second and fourth days after the initial injection. The result is often dramatically satisfactory.

#### USE OF COMBINED ANTIGENS

There is ample evidence to prove both the feasibility and the value of combinations of the various antigens used in immunizing children. As a matter of fact, such combinations are not to be regarded as experimental. In 1939, Ramon<sup>4</sup> demonstrated that not only could an animal be immunized with several of these antigens simultaneously but that there was an actual synergistic effect when certain antigens were given together. For example, he and others have demonstrated higher levels of antitoxin for both antigens when diphtheria and tetanus toxoids are given simultaneously as compared to their administration separately. Lapin<sup>5</sup> has shown the value of combined alum-precipitated diphtheria, tetanus toxoids in children and Miller and co-workers and others<sup>6</sup> have repeatedly shown the feasibility and desirability of combining diphtheria and tetanus toxoid and pertussis vaccine in a single preparation to be given in two or three injections approximately a month apart. We have for two or three years now been using a triple vaccine containing alum-precipitated diphtheria and tetanus toxoid and pertussis vaccine. Our plan is to

TABLE 5  
*Immunization Schedule*

AGE	ANTIGENS	REMARKS
3 mo.	Triple vaccine (alum) Diphtheria Tox. Tetanus Tox. Pertussis Vac.	0.5 cc. or 1.0 cc. depending on product used.
4 mo.	Triple vaccine (alum) Diphtheria Tox. Tetanus Tox. Pertussis Vac.	0.5 cc. or 1.0 cc. depending on product used.
5 mo.	Triple vaccine (alum) Diphtheria Tox. Tetanus Tox. Pertussis Vac.	0.5 cc. or 1.0 cc. depending on product used.
6-12 mo.	Smallpox Vaccination	Repeat every 5-7 years.
12-18 mo.	Triple vaccine as above Also tuberculin test.	Booster injection.
3 years	Diphtheria and tetanus toxoids.	Second booster dose.
5 years	Diphtheria and tetanus toxoids.	Repeat booster dose Repeat tuberculin test Repeat smallpox vaccination

start immunizations at the third month as indicated in Table 5.

Most of our experience has been with an alum adsorbed vaccine produced by Cutter Laboratories. The fact that infants under six months of age do produce antigens against diphtheria and tetanus and agglutinins against pertussis, is indicated in Table 6.

Laboratory studies in our patients have demonstrated antibody levels well above those ordinarily regarded as indicative of immunity. While we have made no definite organized attempt to follow up patients immunized, no instance of failure of immunization against either of the three diseases, diphtheria, tetanus or pertussis has come to our attention. It is necessary also to mention the matter of reactions since these inevitably come up when one discusses the use of combined antigens. It has been our experience that reactions have been little if any more prevalent following use of combined antigens. Nor have we taken any special precautions such as drawing the triple vaccine from the vial with one needle and then changing it to another for the actual injection as has been recommended by certain investigators. We have attempted in most instances to give a booster dose of the same triple vaccine some 12-18 months after the initial course. We feel certain that by so doing we more than make up for any deficiencies of antibody production which attend the early immunization. It

TABLE 6

*Antibody Levels of 29 Infants Whose Immunization Was Begun at Fourth Month or Earlier With Triple Vaccine (Alum)*

PERTUSSIS AGGLUTININS	
Antibody Levels	Infants
0	0
1:0	4
1:100	3
1:200	8
*1:400	4
1:800	2
1:1600	3
1:3200	5
	—
	29

TETANUS ANTITOXIN	
Antibody Levels (units/cc.)	Infants
0	0
* >.01 <.1	2
>.1 <1.	1
>1.	25
	—
	28

DIPHTHERIA ANTITOXIN	
Antibody Levels (units/cc.)	Infants
0.	0
<.03	1
* >.03 <.1	2
>.1 <1.	9
>1.	17
	—
	29

has been observed by some that whereas infants of two or three months may develop antibodies fairly readily, they may lose these antibodies and their protection after several months. Our recommendations of the booster dose approximately one year after the initial immunizing course takes cognizance of these reports.

### IMMUNIZATION AGAINST TETANUS

The rationale of routine immunization of children against lockjaw is sometimes questioned in view of the low incidence of the disease in the general child population. We sometimes feel that routine use of tetanus toxoid in small children is almost justified for the peace of mind that it affords both the parents and family physician in the management of the many apparently trivial cuts, punctures, and lacerations which the young child encounters in his play. It is also true

\* In each instance the asterisk marks the approximate antibody level which has been found indicative of immunity against the corresponding disease.

that the actively immunized child is much better protected against tetanus than is the one who has just been given 1,500 or 3,000 U.S.P. units of tetanus antitoxin following injury. Antibody levels in the blood are likely to be 5- to 10-fold higher in the actively immunized child who has just been given a booster dose of tetanus toxoid than in the child who has received the above-mentioned dose of antitoxin. It is undoubtedly good practice to have an allergic child actively immunized against lockjaw to avoid the possible ill effects of horse serum administration in case of accidental puncture wounds in the nonimmunized.

### SCARLET FEVER IMMUNIZATION

In most parts of the country routine immunization of children against scarlet fever has been largely abandoned and in view of the effectiveness of both penicillin and sulfonamide drugs against this disease, it seems unlikely that active immunization will be again adopted as routine procedure. Interest has been reawakened, however, by the possibilities of immunization against scarlet fever by the introduction of a new type antigen. We have had some experience with an alum-stabilized toxin, furnished by Lederle Company in the immunization of student nurses and also the inmates of a home for feeble-minded near Ann Arbor. The new antigen is administered by intracutaneous or subcutaneous injections a week apart and has been effective in reversing positive Dick tests in approximately 90 per cent of those injected. There have been no unfavorable reactions, such as frequently characterized the use of the Dick procedure for active immunization. Also, in the two groups which we have immunized there have been no instances of scarlet fever in the past two years; whereas, before that time we had cases occurring each winter. Reversal of a positive Dick test was encountered in practically 100 per cent of instances where four injections of the alum-stabilized toxoid were given.

### DIPHTHERIA

New methods of immunization against diphtheria are proposed from time to time such as administration of the antigen by the percutaneous route and also by intracutaneous injections of clear fluid toxoid. While these are of interest it is probably fair to state that the time-tested method of two injections of alum-precipitated diphtheria toxoid is still the preferred method of immunization. During recent years diphtheria incidence has been at very low ebb in this country but there is evidence from almost every state that the disease may be assuming greater virulence than hereto-

fore, inasmuch as the attack rate in children previously immunized is becoming greater. Two lines of defense against the disease are clearly indicated. The first involves continuing efforts on the part of public health officials, school health authorities, parents and physicians to see that at least 70 per cent of all the young children in any community are immunized. The second involves the more frequent use of the Schick test and the booster dose of diphtheria toxoid to insure the high level of protection at least during the school years. It has been our practice to give the initial course of immunization against diphtheria along with pertussis and tetanus during the first year and repetition of a booster dose of the same vaccine during the second year followed by a booster dose of diphtheria and tetanus toxoid at two- or three-year intervals. If such practice could be applied to 75 per cent or more of the children in all communities, diphtheria would very quickly disappear as a clinical disease.

### MEASLES AND MUMPS

There is good reason to expect development of active immunization against measles in the near future. The promising work of Stokes in this connection was interrupted by the war. In the meantime the gamma globulin fraction of pooled adult blood has proved very efficacious in the prevention or modification of measles. In amounts ranging from 0.5 cc. to 5 cc., depending on the age of the child, gamma globulin has proved very useful in modifying the severity of measles or in preventing it entirely. Use of gamma globulin in children under four years, and particularly in children known to have had tuberculosis, is strongly recommended. Gamma globulin has recently been widely available through the American Red Cross which has distributed the product without charge to health departments. Adequate instructions for use of gamma globulin are contained with each 5 cc. ampule of the product.

This is the same gamma globulin which has been demonstrated to confer passive immunity against in-

fectious hepatitis, and there is some evidence that it may be helpful in preventing mumps orchitis in post-puberal males. For a discussion of these uses of gamma globulin the reader is referred to the writings of Havens, Paul<sup>9</sup> and others (prevention of infectious hepatitis) and Gellis, McGuinness and Peters<sup>10</sup> (prevention of mumps orchitis). Active immunization against mumps, still in the stage of clinical trial, is promising. The reader is referred to the work of Stokes and co-workers<sup>11</sup> in this connection.

### SUMMARY

Changing practices in immunization include earlier immunization particularly against whooping cough; the tendency to use multiple antigens, particularly combinations of diphtheria and tetanus toxoid with pertussis vaccine; and the use of alum to precipitate, adsorb or stabilize antigens so as to prolong their action and thus obtain higher antibody levels. The use of the booster dose to maintain high antibody levels and to enhance protection particularly when epidemics threaten is increasing. The recent war has greatly increased interest and confidence in active immunization as a means of controlling certain diseases.

### BIBLIOGRAPHY

1. Sauer, L.: *Am. J. Dis. Child.*, 61:656, 1941.
2. Fox, M. J., and E. M. Knott: *J. Pediat.*, 24:671, 1944.
3. McGuinness, A. C., W. L. Bradford, and J. G. Armstrong: *J. Pediat.*, 16:21, 1940.
4. Ramon, G.: *Internat. Clin.*, 1:241, 1939.
5. Lapin, J. H.: *J. Pediat.*, 22:439, 1943.
6. Miller, J. J., Jr., J. B. Himber, and J. O. Dowrie: *J. Pediat.*, 24:281, 1944.
- Hamilton, P. H., and E. G. Knouf: *J. Pediat.*, 25:236, 1944.
7. Gibbard, J., E. T. Bynoe, and R. J. Gibbons: *Canad. J. Pub. Health*, 36:188, 1945.
8. Mattson, B. F.: *New York State J. Med.*, 44:2063, 1944.
9. Havens, W. P., Jr., and J. R. Paul: *J. A. M. A.*, 129:270 (Sept. 22) 1945.
10. Gellis, S. S., A. C. McGuinness, and M. Peters: *Am. J. M. Sc.*, 210:661-664 (Nov.) 1944.
11. Stokes, J., Jr., et al.: *J. Exper. Med.*, 84:407 (Nov. 1) 1946.

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### Prevention of Rust on Instruments

If instruments are taken from the sterilizer promptly there is little opportunity for the formation of rust. However, this is not always possible in the office of a busy practitioner. Add from 1 to 2 Gm. of borax for every 100 cc. of water in the sterilizer and no rust will occur even if the instruments are immersed in it for weeks. Borax can also be added to most disinfecting solutions for rust prevention.



*A rapid heart may, or may not, reflect cardiac disease. If it does, treatment should be instituted and differs, depending on the type of rapid heart beat present. In many cases electrocardiograms are not needed for the differential diagnosis.*

## Diagnosis and Treatment of Tachycardias\*

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It is well known that tachycardia should include any cardiac mechanism in which the rate is above 100 per minute. This figure is arbitrarily selected by the American Heart Association. Therefore, this discussion will include any cardiac mechanism which may have a rate over 100 with either regular or irregular rhythm.

Any discussion of tachycardias should be prefaced with the thought that tachycardia in itself may not be of any significance, since in many cases it is not an indication of heart disease and does not indicate any adverse prognosis. The object of paramount importance, then, in any given case presenting a tachycardia is to decide whether or not it is indicative of heart disease. This decision may be aided by the presence or absence of other physical findings which accompany definite organic heart disease and a positive or negative history suggesting cardiovascular disease. It is important to diagnose the type of arrhythmia so that proper therapy may be instituted. The necessity of machines of precision in diagnosing arrhythmias has been overdone. Many practitioners have been led to rely on electrocardiograms and have lost some of their technical skill in bedside diagnosis of arrhythmias. Many cases of tachycardia may be diagnosed by astute and careful clinicians. However, in uncertain cases an electrocardiogram is a great necessity. There are occasions when a routine electrocardiogram may not supply the final diagnosis, and then more intensive electrocardiographic surveys such as esophageal leads may be necessary.

### SINUS TACHYCARDIA

Sinus tachycardia is rapid heart action with a regular rhythm. The rate in adults ranges between 100 and 160. This may be higher in children or infants. Sinus tachycardia over 160 is rarely found in adults. It is the most common disorder of the cardiac mechanism that is not associated with actual organic heart

disease. It may be brought on by exercise, excitement, anxiety, certain medications such as atropine and nitrites, nervousness, fever, and hyperthyroidism. It becomes a significant disturbance of the cardiac mechanism when it is prolonged in cases of myocardial weakness or failure. Its persistence is undesirable in cases of congestive failure; and it is an indication of poor prognosis if it persists longer than a week following a myocardial infarction.

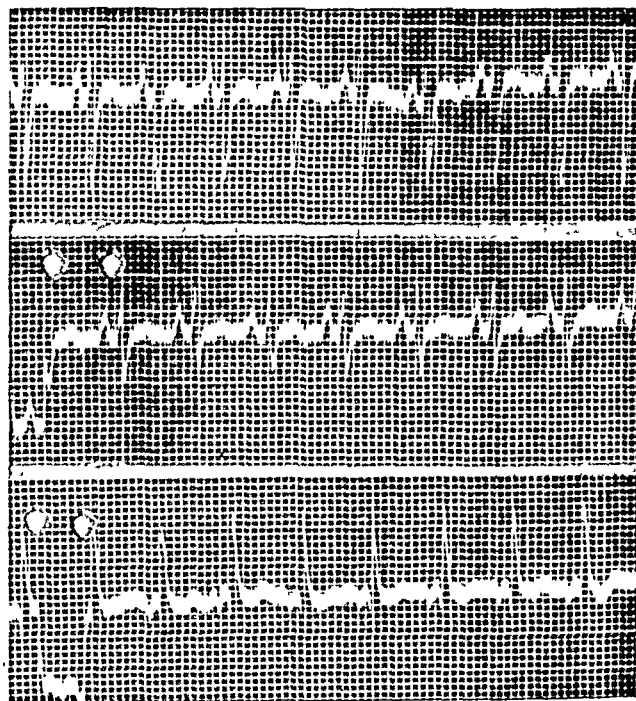


FIG. 1. Electrocardiogram showing sinus tachycardia in a child with a vertical type small heart.

Sinus tachycardia is easily diagnosed clinically in most cases without the aid of an electrocardiogram. If there is any doubt in differentiating it from other tachycardias with regular rhythm, carotid sinus pressure is the clinical procedure most helpful. Carotid sinus pressure will cause a very conspicuous momentary slowing according to a definite ratio if the

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tachycardia is due to auricular flutter, or it will cause an *abrupt cessation* of the tachycardia if it is due to auricular paroxysmal tachycardia. If carotid sinus pressure has no influence on the tachycardia of regular rhythm, then it is necessary to rely on an electrocardiogram for differentiation.

Since this disturbance of cardiac mechanism is frequently not associated with organic heart disease, there is no specific therapy. Of course, the etiologic agents should be eliminated; and if the tachycardia is due to diseased states outside the cardiovascular system, therapy for these conditions should be instituted. If the tachycardia is due to congestive failure, the usual treatment for congestive heart failure is indicated. If it accompanies coronary insufficiency or myocardial infarction, vasodilating drugs such as aminophylline should be used. In cases of persistent sinus tachycardia or frequent paroxysms of sinus tachycardia without any evidence of organic heart disease, vagal stimulants such as prostigmine by mouth or injection may be helpful.

#### PAROXYSMAL AURICULAR TACHYCARDIA

Next in frequency of occurrence is paroxysmal auricular tachycardia. This is the most common of the ectopic tachycardias. It probably occurs more fre-

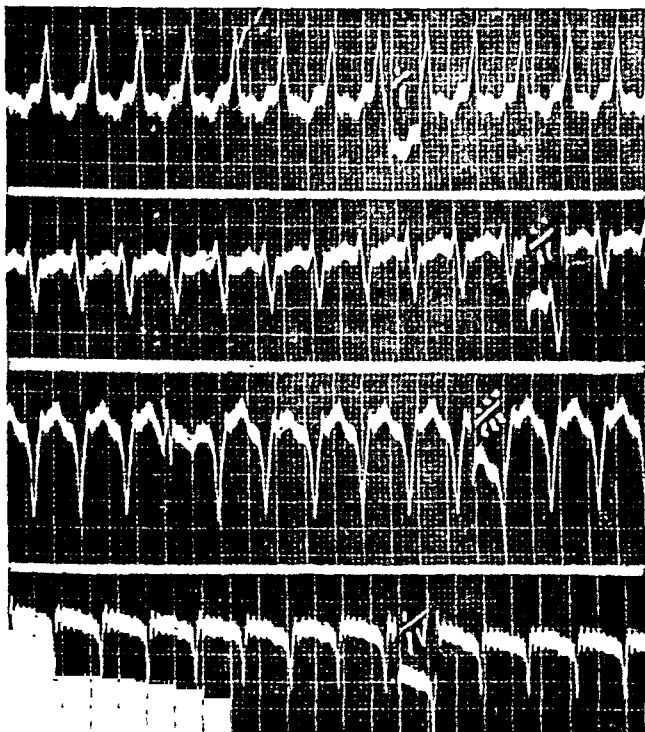


FIG. 2. Electrocardiogram showing an attack of paroxysmal auricular tachycardia. This tracing indicates the effect of left ventricular strain as a result of continued tachycardia.

quently than has been recorded because many normal persons may have short paroxysms of tachycardia lasting a few seconds and these are not sufficiently troublesome to excite concern on the part of the person affected. Also the brevity of the paroxysms make it impossible to obtain electrocardiographic evidence in many of the cases. It is an ectopic rhythm which occurs in many normal persons and is more common in adults than in children. It would be impossible to name all the exciting factors of paroxysmal auricular tachycardia. The most common are effort, excitement, excessive use of stimulants, thyrotoxicosis, and organic heart disease, especially mitral stenosis. Only a small minority of the persons who have this tachycardia actually have heart disease. However, if we compare the relative incidence in normal persons and in cardiac patients, there is usually a higher incidence in the cardiac patients.

As far as prognosis is concerned, paroxysmal auricular tachycardia is unimportant, although it may be quite disagreeable to the patient. An exception to this rule is its occurrence in the presence of heart disease. If it occurs in mitral stenosis, the pulmonary circulation is engorged and marked dyspnea and even severe cardiac asthma may result. If it occurs in heart disease where there is enlargement of the left ventricle, left ventricular failure and pulmonary edema may result. If it occurs in cases of coronary insufficiency, a severe attack of angina may ensue. Rarely congestive failure may develop in normal persons if the attacks are of long duration.

The diagnosis can usually be made without any electrocardiographic evidence. The sudden onset and usually sudden cessation, with the rate varying between 160 and 200, and a duration of a few minutes to a few hours is enough evidence to make the diagnosis. Sometimes the attack does not end abruptly, because when the heart resumes its normal rhythm, the sinoauricular rate may be elevated by the excitement of the attack or otherwise and thus prevent the sensation of a marked change in heart rate. One rather definite method of clinically diagnosing this arrhythmia is that of vagal stimulation. This can be accomplished by a number of mechanical techniques, but the most effective is usually by gagging the patient. This will result in a sudden cessation of the paroxysm. No other tachycardia will respond in such a manner.

The treatment of paroxysmal auricular tachycardia is usually simple. Rest at the time of the paroxysm, reassurance, and the omission of any exciting factors are sufficient to prevent recurrent paroxysms. In many cases the paroxysms are so brief that therapy is not indicated. In most cases, during the attack some

mechanical form of vagal stimulation is all that is necessary. In the more persistent or intractable cases, quinidine sulphate is most commonly used. It may be administered by mouth in 3 to 6 gr. doses (0.2–0.36 Gm.) and repeated several times at two-hour intervals. It can also be given intramuscularly as quinine dihydrochloride. In a number of cases, digitalization is effective. Other drugs such as magnesium sulphate intramuscularly have been recommended, but in our experience have not been very effective. Vagal stimulants such as mechoyl have been used to stop obstinate attacks. This drug is injected subcutaneously in doses of 20 to 50 mg. This should be used with great caution because being a powerful vagal stimulant it may produce pulmonary edema. When it is used, atropine sulphate, gr. 1/60 (1.0 mg.) should be at hand for immediate intravenous use in cases in which undesirable reactions develop.

### AURICULAR FIBRILLATION

Auricular fibrillation is a disturbance of cardiac mechanism in which there is a circus wave in the auricle at the rate of 450 to 600 per minute. Its circular pathway is apparently irregular, and it is always accompanied by an irregular ventricular response. The ventricular rate varies between 120 and 150 and is absolutely irregular. It is infrequently found in the absence of heart disease. There have been reported cases of paroxysms of auricular fibrillation in persons with normal hearts.

It has been demonstrated by observations on dogs that three requisites are necessary for the development of fibrillation.<sup>1</sup> These are enlargement of the left auricle, anoxia of the auricular musculature, and vagal stimulation. Therefore, the most permanent underlying factors are mitral stenosis, thyrotoxicosis, hypertension, and coronary artery disease. In the paroxysms which occur in normal individuals, the factors which play a role in its production are excitement, sustained effort, and stimulants.

This arrhythmia is easily diagnosed in most cases because it is grossly irregular without any basic rhythm and in untreated cases there is frequently a pulse deficit. It may sometimes be difficult to differentiate from frequent premature contractions in which case an electrocardiogram may be necessary. If the patient can exercise, it is clinically possible to differentiate these two arrhythmias. After exercise the premature contractions are apt to disappear and the rhythm will be regular while in auricular fibrillation the rhythm becomes more irregular.

The prognosis in this disturbance of cardiac mechanism usually depends on the underlying heart condi-

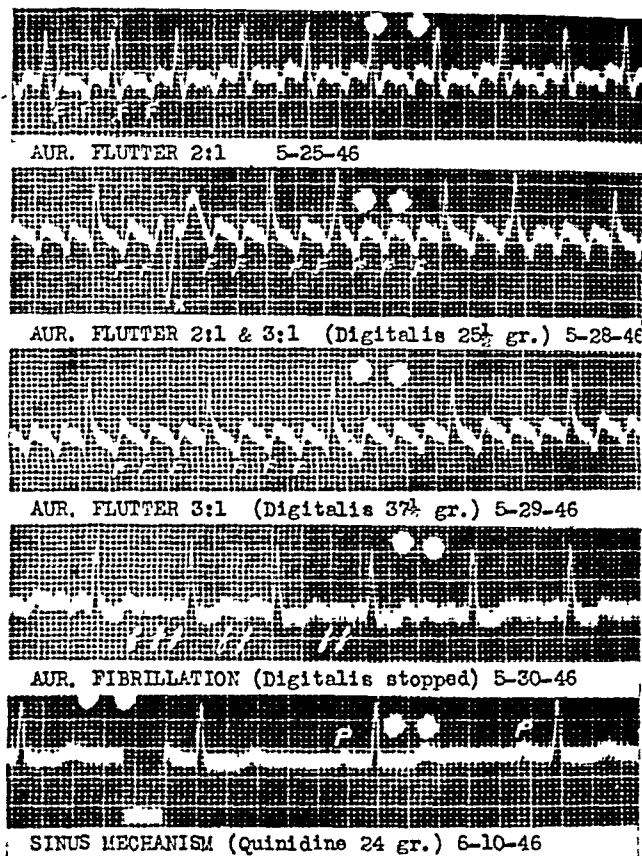


FIG. 3. This electrocardiogram shows the characteristic findings of auricular flutter and auricular fibrillation. It also indicates the proper therapeutic management of auricular flutter.

tion. In the absence of heart disease, the prognosis of the paroxysms is excellent and the attack usually subsides spontaneously.

In most cases the treatment of auricular fibrillation is digitalization; however, if the arrhythmia has been present for only a short time, then the use of quinidine is the best measure. Quinidine will stop the paroxysm, thus resulting in a normal sinus mechanism. If, on the other hand, the arrhythmia has been of long standing, there may be danger in the use of quinidine in that some patients may develop embolic phenomena due to emboli breaking off from the auricular appendages when sinus mechanism is re-established. In a few cases of auricular fibrillation the rate may be slow enough to provide an efficient circulation so that no therapy is required at all. This is true if there is an absence of congestive failure and a relative freedom from the symptoms of cardiovascular disease. If the fibrillation is due to thyrotoxicosis, adequate treatment of the thyrotoxicosis is usually sufficient to stop this arrhythmia. If marked congestive failure develops as a result of thyrotoxicosis, then digitalization is

indicated. It should always be remembered, however, that digitalis does not stop auricular fibrillation. This is especially true in thyrotoxicosis where digitalis may not always be effective in reducing the ventricular rate to normal levels as it does in most other cases of auricular fibrillation accompanying other types of heart disease. If auricular fibrillation and congestive failure occur in cases of myocardial infarction, the most useful treatment is a combination of digitalization and quinidine.<sup>2</sup> According to recent reports, this is more effective than using either quinidine or digitalis alone, or in not using either one of the drugs. It would be well to suggest here that the use of quinidine is effective only if adequate doses are administered. We have found on repeated occasions that large doses, as high as 45 to 50 gr. (3.0–3.3 Gm.) of quinidine a day, may be necessary to stop fibrillation.

### AURICULAR FLUTTER

Auricular flutter is related to fibrillation in that it is a result of a regular circus action in the auricle, probably in the neighborhood of the sinus node. Its rate is usually 200 to 300 per minute, and the ventricular rate is usually half that of the auricular rate due to the occurrence of a two-to-one block. It is extremely rare to have a one-to-one rhythm in cases of auricular flutter. This disturbance in cardiac mechanism is relatively uncommon.

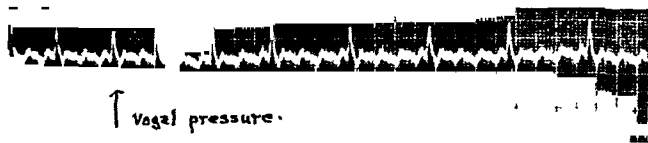


FIG. 4. This indicates the effect of vagal stimulation on auricular flutter. It changes from a 2:1 to a 4:1 flutter with exact halving of the ventricular rate.

In most cases of auricular flutter, there is an organic heart disease. It is most common in cases of a mitral stenosis with a buttonhole mitral valve, or in other words, a tight mitral valve. It may occur in coronary artery disease and occasionally occurs in normal individuals. The positive diagnosis of this arrhythmia can be made clinically in only one way; namely, temporarily halving of the heart rate by carotid sinus pressure. This differentiates it from paroxysmal auricular tachycardia and sinus tachycardia. In most cases, the attacks of auricular flutter are more prolonged than those of simple paroxysmal auricular tachycardia.

The prognosis usually depends on the associated

heart disease which is responsible for the disturbance of cardiac mechanism.

The treatment is usually simple, with digitalis being the drug of choice. Large doses of digitalis will result in an increase in the rate of the circus movement, thus resulting in auricular fibrillation. If the digitalis is stopped when fibrillation occurs, then a normal sinus mechanism should follow. If this does not occur, quinidine is necessary to stop the auricular fibrillation.

### VENTRICULAR PAROXYSMAL TACHYCARDIA

Ventricular paroxysmal tachycardia is much less common than auricular paroxysmal tachycardia. It is similar in mechanism to auricular paroxysmal tachycardia except that the impulses originate in the ventricular muscle or in the bundle branches. It is a disturbance of cardiac mechanism associated with organic heart disease or toxic states. It is an extremely rare occurrence in normal individuals. The two most important etiologic factors are recent myocardial infarction and digitalis poisoning of high degree. The diagnosis may be suspected in patients who have a heart rate of about 160 and a regular rhythm, and in whom there is a history of a recent myocardial infarction or a history of excessive use of digitalis. The diagnosis

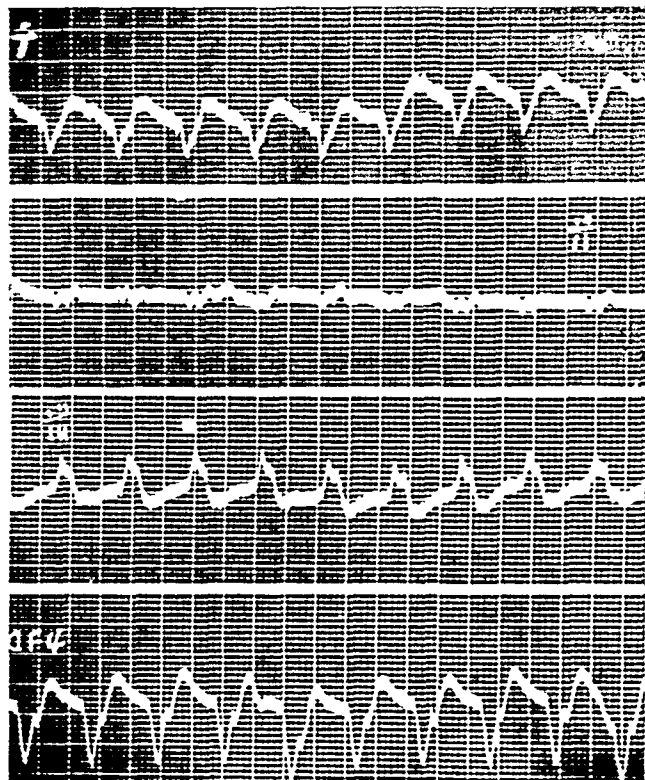


FIG. 5. This demonstrates the bizarre QRS complexes and typical tracing of ventricular tachycardia.

can be made with certainty only by an electrocardiogram.

This disturbance of cardiac mechanism usually carries with it an unfavorable prognosis, because in most cases it accompanies severe underlying heart disease.

The treatment of ventricular paroxysmal tachycardia is the administration of quinidine in addition to the usual measures taken in the treatment of heart disease, such as bed rest, oxygen, etc. It is highly important that quinidine be used in adequate doses to cause a cessation of this tachycardia as soon as possible. When the tachycardia has been arrested, it may be and frequently is advisable to continue a maintenance dose of quinidine in order to prevent further recurrences. In cases of recent myocardial infarction, this is especially true. In these cases, it should be continued until healing of the infarcted area has been completed.

## SUMMARY

A discussion of the characteristic clinical and diagnostic findings in the disturbances of cardiac mechanism producing tachycardias is presented. The clinical differential diagnosis of the tachycardias is emphasized. The role of carotid sinus pressure in differential diagnosis is stressed. Electrocardiograms are the last word in the diagnosis of tachycardias when the clinical findings are not definite. Effective therapeutic procedures in correcting the abnormal cardiac mechanism are discussed.

## BIBLIOGRAPHY

1. Smith J. R., and K. S. Wilson: Studies on the production and maintenance of experimental auricular fibrillation, *Amer. Heart J.*, 27:176-185, 1944.
2. Askey, J. M., and O. Neurath: The treatment of auricular fibrillation occurring with myocardial infarction, *Amer. Heart J.*, 30:253-259, 1945.

## Medical Journalism in 1848

... The general plan of the original periodical publications which have been enumerated is very similar. The first part of each number is devoted to original articles, consisting of essays, histories of epidemics and endemics, series of cases, and single cases, and accounts of operations. Occasionally a more detailed and comprehensive history of some disease is introduced under the name of *monograph*, and not unfrequently extensive statistical tables are given, bearing especially upon surgical and obstetrical practice. Then follow *Reviews* or formal examinations of works recently published, usually analytical in character, and having for their principal object the book rather than the general subject of which it treats. To this division succeeds a miscellaneous and heterogeneous assemblage of *bibliographical notices*; the sweepings of the critical *atelier*; the rinsings and heeltaps of the critical banquet; a necessary part of the editor's prospectus, but one which is least gratifying to minute inspection. Here the importunate friend receives his expected compliment, the dull dignitary is pacified with his scanty morsel of eulogy, the Maecenas is paid in fair words for his patronage; the book which must be noticed and has not been read, is embalmed in safe epithets and inurned in accommodating generalities. Lastly, a considerable part of the number is made up of selections, either taken promiscuously from other journals and recently published works, or in the better managed periodicals classified so as to present a

summary of the recent progress of science in its several departments.

The proportion allotted to these several divisions varies very much. Taking into consideration the usual difference of type in the original and borrowed matter, and the very liberal extracts which the reviewers commonly make from the work before them, it will be found that a very large part of all the journals is made up of quotations; and to a considerable extent of the same quotations, whatever may be the particular journal examined. The committee have been struck with the fact, that the same articles have been presented over and over again to their notice, in many different periodicals, each borrowing from its neighbours the best papers of the last preceding number, so that the perusal of many is not so much more laborious than that of a single one, as would be anticipated. The ring of editors sit in each other's laps, with perfect propriety, and great convenience it is true, but with a wonderful saving in the article of furniture.

—From the report of the committee on medical literature. *Transactions of the American Medical Association*, Vol. 1, 1848, pp. 255-256. The committee was composed of Oliver Wendell Holmes, Enoch Hale, G. C. Shattuck, Jr., D. Drake, John Bell, Austin Flint and W. Selden.

*Of all symptoms headache is perhaps the most varied in its meaning. Certainly it is one of the most common and frequently the most distressing. This article gives some pointers on differential diagnosis and describes in detail some newer methods of treatment of some varieties of headache.*

## Headache: Common Etiologic Types and Methods of Therapy\*

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Headache is one of the most frequent of all medical complaints. It may be caused by so many different organic or psychologic conditions that it takes a complete medical workup to properly diagnose the cause. As Woltman has pointed out<sup>1</sup> headache, oftener than not, is a symptom that occurs without signs. Therefore, physical and neurologic examinations are usually normal. This leads to the conclusion that an accurate detailed history is the most significant factor in our proper diagnosis of "headache."

In dealing with this subject we must not overlook serious organic lesions that may be causing headache as one of the earliest manifestations. Nor must we forget that a patient may have more than one type of headache, one of which may be trivial while the other may accompany a fatal illness. Once the diagnosis is made, the problem of treatment may be approached with much more optimism than in former years, for there is usually much that we can do for these unfortunate patients.

In approaching the problem, inquiry should be made as to the length of time the patient has had the complaint. As is true of complaints elsewhere in the body, a patient that appears well after many years of the same complaint is less likely to have serious organic disease than is one who has recently acquired the symptom. Of importance also are the frequency, duration, location and the hour of day or night on which they may occur, the effects of emotional or physical exhaustion, eyestrain, indulgence in certain foods or alcohol. Is there an aura in any shape or form? Is there a family history of headache, epilepsy, urticaria, eczema, asthma, hay fever or vertigo? Do changes in temperature or humidity affect the patient? Is there concomitant infection of the nose or ears or elsewhere in the body? Of what influence have been menstruation and pregnancy? Are the headaches improving or not? What associated symptoms occur

with the headaches, such as nausea, emesis, photophobia, lacrimation, nasal congestion, scotomata, paresthesias or paralysis?

In addition to an accurate history, complete physical and neurologic examination, each patient whose headache does not appear to be an acute, easily handled illness, should have further diagnostic studies. Among these are roentgenograms of the skull, examination of the ocular fundi and, in certain cases, x-rays of the cervical spine, the sinuses and the teeth. Where indicated, electroencephalograms, air encephalograms and spinal fluid examinations should be performed.

It must be realized that headache is a common symptom in many systemic diseases. In some it is but a secondary symptom to be treated symptomatically. Discussion will be limited to certain conditions in which it is one of the major features or in which it requires specific treatment. The serious organic lesions will be considered first and the functional syndromes later. True tics or neuralgias, most of which are approached from a neurosurgical standpoint, will not be discussed.

### HEADACHE OF INCREASED INTRACRANIAL PRESSURE

In this category fall the most serious conditions in our discussion: organic intracranial disease, brain tumors, abscesses and cysts. These are often accompanied by vomiting of the projectile type, progressive loss of sight, lessening of motor and sensory functions and changes in personality. The clinical picture can be so varied that it may not follow classical lines. However, the following features often suggest it: A relatively recent onset with increasing discomfort; the pain recurring periodically in the same location; pain which awakens the patient early in the morning, has sudden onset and termination and is accentuated by stooping, straining or shaking the head; a pulse which becomes slow or irregular at times. When an intracranial lesion is suspected or if headache is accompa-

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ried by any of the above features, no time should be wasted in instituting proper neurologic examination as described above. We must not neglect to x-ray the chest and to perform a thorough physical examination to avoid performing craniotomies on patients in whom a tumor may be metastatic from the lungs or other sites. There should be no hesitation in recommending proper surgical procedures once a diagnosis of cyst, abscess, tumor or hematoma has been made.

#### HEADACHES ASSOCIATED WITH DECREASED INTRACRANIAL PRESSURE

These often occur in central nervous system arteriosclerosis. They occur when the patient is up and about and leave when he lies down and may resemble a spinal puncture headache. These are often helped by vasodilating drugs; one of the most popular now is nicotinic acid administered orally one to four times a day. The dose ranges from 25 to 100 mg. and should be sufficient to produce a generalized flushed sensation. Mild sedation three times a day or an analgesic such as empirin compound control many of these headaches.

#### HEADACHE ASSOCIATED WITH RUPTURED INTRACRANIAL ANEURYSM

These usually occur in young adults and may be preceded by vague headache for several days or months. Rupture often occurs after sudden physical exertion and causes an excruciating occipital headache. There may be signs of meningeal irritation due to free blood in the subarachnoid space. If the patient recovers, paresis of the third cranial nerve on the same side and hemiplegia on the other is often found. If the diagnosis can be accurately made, ligation of the internal carotid artery after proper preparation should be done. It might be wise to point out that if we are to ever diagnose these before rupture we must look for them. This diagnosis should be considered in every case of migraine constantly localized on the same side and followed by ocular paresis. If suspected, we can inject thorotrast into the common carotid artery and take roentgenograms which may show the aneurysmal dilatation of the artery, usually in the circle of Willis.

A similar story but with a lateralized headache and often with less evidence of meningeal irritation in a person with hypertension suggests a cerebral hemorrhage.

#### HYPERTENSIVE HEADACHE

These are in the occipital or frontal regions. They occur on awakening but usually do not awaken the

patient. In association with migraine they may be very disabling. The treatment is that of the hypertension with restriction of fluid and salt and elevation of the head of the bed. Many obtain relief with potassium thiocyanate as will be discussed below. Many patients who have had a sympathectomy for their hypertension will be relieved of the headaches, even if the blood pressure is not lowered by the operation.

#### POST-TRAUMATIC HEADACHE

These often occur after trivial injuries. The main point in treatment is the settlement of the question of damages after making certain that no organic lesion exists. These situations often must be approached from a psychiatric point of view. One should always be on the lookout for subdural hematomata in patients with a history of head injury.

#### TOXIC HEADACHES

These occur in infectious diseases, nephritis and many febrile conditions. They cause dull frontal headache such as one gets with fever. Treatment is that of the underlying condition.

#### SPECIAL SENSES

Eyestrain due to refractive errors may cause frontal, parietal or orbital pain.

Ear Pain. We usually get a lead from a history of ear infection. We must look for complications when there is prolonged pain after an ear infection. Bear in mind the possibility of extension to the mastoid and even intracranial bones and spaces.

Nose and Sinuses. Usually those ear, nose and throat conditions with pain are acute inflammations<sup>2</sup> and we are led to the diagnosis by the history of a recent upper respiratory infection. An accurate ear, nose and throat investigation will determine which sinus is involved and then provision of proper drainage of that sinus is indicated. Allergic sinus disease may rarely produce headache by pressure of the edematous tissues on the ostiae of the sinuses with retention of secretions. Specific allergic states may at times be found but many will be cases of physical allergy.<sup>3</sup> Some respond to histamine desensitization and there is now promise that antihistamine preparations such as benadryl<sup>4</sup> and pyribenzamine may act favorably in these patients.

#### RHEUMATIC HEADACHES

These may cause long lasting, constant occipital or nuchal pain. Palpation reveals tender indurated



areas in the muscles of the neck and scalp and pressure over these may produce attacks. Injection of saline into these areas will often produce an attack and injection of novocaine will relieve it. Distribution of the pain is according to muscle and not nerve, unless the nodule happens to compress a nerve running through the muscle, in which case one gets a true neuralgia. Because of these features, Williams<sup>5</sup> has given this condition the name of myalgia of the head. Attacks may be precipitated by exposure to cold or any stimulus which increases tension of the muscles. Some cases seem to be on an allergic basis due to physical irritants such as changes in temperature, atmospheric pressure or humidity. Emotional tension may bring on attacks. It has been shown that these states of physical allergy may be associated with an actual increase in histamine content of the circulating blood.<sup>5</sup> Most of these were formerly misdiagnosed as "sinus headaches." Relief may be had by one of the three following methods of treatment: (1) Heat and massage. Use general massage over the entire scalp and nuchal areas and firm friction massage over nodules. These patients may need many such treatments. (2) Histamine desensitization. (3) Nicotinic acid; start with 25 mg. twice daily, orally, and then increase to 100 mg. and maintain for two to three months. After that relief can usually be maintained with 100 mg. three times a week.

#### HEADACHES ASSOCIATED WITH PSYCHO- NEUROSIS OR NERVOUS EXHAUSTION

These occur constantly for months at a time and are poorly defined. They are described as a band-like, heavy weight, pressure, or pulling sensation. Other signs of psychoneurosis are often present. A complete lack of any features characterizing them as another type of headache helps in the diagnosis.

#### MIGRAINE

Migraine is the most common type of periodically recurring headache. My own files reveal that 20 per cent of all patients visiting the office for varied complaints have or have had migraine headaches. By migraine we mean periodic, unilateral, temporal or orbital pain with definite hereditary background of either headache, epilepsy or definite allergy. They are often preceded by an aura in the form of scotomata, mental dullness, or blurred vision and are accompanied or followed by nausea and often emesis. They are at least twice as frequent in women as in men and usually attack the ambitious members of

society. They appear under periods of stress or in definite relation to the menstrual period and in many disappear during pregnancy and at the climacteric. Ninety per cent of the attacks are relieved by injections of 0.5 mg. of ergotamine tartrate, which thus may be used as a therapeutic test.

The history of the therapeutic approach to the migraine problem shows that very few stones have been left untouched in attempts to control the malady. More emphasis is being placed on functional and emotional aspects<sup>7</sup> and indeed many of these patients may receive relief by psychiatric treatment and release from nervous tension. It is well to attempt to ferret out each patient's difficulties and endeavor to teach him how to avoid strains and situations that will lead to the migraine attack. However, in spite of the above, many will continue to have the seizures and other methods will have to be used.

In discussing the treatment of migraine we must distinguish between treatment of the individual attack and prophylaxis to avoid getting an attack. Most patients say they are more comfortable if, when they feel an attack coming on, they can lie down in a quiet, dark room and hold a cold towel tightly against the pulsating temporal artery on the affected side. It often helps to take aspirin, empirin or sedatives. In this way many can weather the storm quite comfortably, but few actually reduce the duration of each attack. There are two more or less specific methods of treatment in use. One is inhalation of 100 per cent oxygen as first introduced by Alvarez.<sup>8</sup> Since 1926 we have had the ergotamine tartrate treatment which if taken early in the attack, will often abort the attack or shorten it. However, many patients have uncomfortable and even dangerous side effects from this. In spite of this many continue to take it by hypodermic injection year after year.

Recently we have investigated a new ergot preparation, "D.H.E. 45" (dihydroergotamine),\* which when used hypodermically in the same dosage as gynergen (ergotamine) (0.5-1.0 mg.) works as well and has many less side reactions. There are no reports of effects on the uterus or an increase in blood pressure. Horton, Peters, and Blumenthal<sup>9</sup> first reported their results in 1942.

In a review of my more recent cases of typical migraine I have summarized my results of treatment with dihydroergotamine in 51 patients.<sup>10</sup> These patients were treated during 266 individual attacks of migraine. In each case, dihydroergotamine was given subcutaneously in doses of 1 cc. (1 mg.). On occa-

\* Supplied for clinical trial by the Sandoz Chemical Works, Inc., New York 14, N. Y.



sion it was found that optimal results were obtained if this same dose was repeated within several hours. In 93 per cent of the attacks the results were excellent, in 1 per cent they were good and in 6 per cent little or no relief was obtained.

We have also studied the effects of the new antihistamine preparation, benadryl, on acute attacks of migraine headaches. Each patient was instructed to take 100 mg. of benadryl orally at the onset of a headache and to repeat within four hours if necessary. Of the eleven patients treated in this manner, four reported marked relief, two moderate relief and five little or no relief.

What can be done to prevent or reduce the incidence of these attacks? As stated above, everything *under the sun has been tried*. Occasionally, by elimination diets and by diaries we can determine that the patient is actually sensitive to certain types of food. Control of ovarian or thyroid dysfunction may control attacks. Some few patients may benefit by prevention of sodium and fluid retention. This is the case in certain women who have migraine with menstruation and who also may have an inordinate craving for salty and spicy foods. In those cases where all the indicated studies have been made and none of the above factors play a part, there are still other things that are often effective.

Hines and Eaton<sup>12, 13</sup> noted that 80 per cent of one of their hypertensive series had migraine and that some of their patients under treatment with potassium thiocyanate for hypertension volunteered that the migraine was improved, even if the blood pressure was not. They found that approximately 80 per cent of their patients with migraine and increased blood pressure received partial or complete relief of headaches on potassium thiocyanate treatment if the blood levels were kept at 10 to 12 mg. per cent. They then studied its effect on patients without elevated blood pressure and of these some 50 to 75 per cent obtained considerable relief.

Another promising approach to the problem is the treatment with histamine. There is considerable evidence to support the theory that migraine in many cases may be precipitated by the release of histamine into the blood stream in patients who have a lowered tolerance to the drug.<sup>14, 15</sup> The debate could go on at length as to where the histamine comes from and why and how it causes migraine. It must suffice at present to present the technic of administration and results of this treatment. Horton<sup>16</sup> first tried histamine, by subcutaneous desensitization as will be described later, with very little success in typical migraine. Since then he has had more success with

prolonged intravenous administration of the drug combined with subcutaneous administration.<sup>17</sup> Butler and Thomas<sup>15</sup> in May 1945 reported on the intravenous administration of histamine in 34 patients with migraine. They used 2.75 mg. of histamine acid phosphate in 500 cc. of normal saline and administered it over a period of four to eight hours. Thirty-one patients obtained complete or considerable relief. I personally give the treatment for a one-hour period in the office daily or every other day and have had very promising results to date.

I have designed my treatment so that the patient may be treated as an ambulatory patient in the office. At the onset I give a daily continuous intravenous drip of histamine diphosphate (2.75 mg. dissolved in 500 cc. normal saline) for four consecutive days. Each treatment is given for approximately one hour at a speed just fast enough to produce a slight flushed sensation about the head without causing uncomfortable side effects (5 to 15 drops per minute). After the initial four days of treatment, the infusions are given three times a week until definite improvement takes place. In successful cases this often occurs at about the third or fourth week of treatment. At this stage subcutaneous administration of histamine as described by Horton<sup>16</sup> is instituted and the intravenous therapy is discontinued. I have found that future relapses may be prevented in many cases by having the patient continue his subcutaneous histamine indefinitely.

### HISTAMINIC CEPHALGIA

In 1939, Horton<sup>16</sup> first recognized a new entity which had long been mistaken as a variant of migraine. This is erythromelalgia of the head, histaminic cephalgia or Horton's headache. This is one of the most dramatic syndromes that I have ever witnessed. It is "classic in its symptomatology and unique in its response to histamine therapy."

Histaminic cephalgia is a unilateral vasodilating head pain usually beginning after the age of 30, which commences and ends suddenly, lasts one hour or less, often awakens the patient one or two hours after retiring and may be eased by standing erect. There is associated profuse watering of one eye, rhinorrhea or stuffiness of one nostril, increased redness and surface temperature of one side of the head and often swelling and tenderness of the temporal artery. Pain is constant and excruciating and involves the eye, temple, neck and face. There is no hereditary background, nausea, or scotomata and this type of headache occurs predominantly in males. Compression of the temporal or carotid artery, application of

cold to the head, immersion of the hands in ice water and intravenous administration of adrenalin may stop the attack. Alcohol ingestion may precipitate the attack. Typical attacks can be produced by injection of 0.1 to 1.2 mg. histamine diphosphate subcutaneously. Treatment is by subcutaneous desensitization with histamine as follows:

The contents of a 1 cc. ampule of histamine diphosphate (0.275 mg.) is equivalent to 0.1 mg. of histamine base. Ampules of this character are now on the market. (All doses are given subcutaneously.) The quantity given at each injection is as follows: first injection, 0.25 cc.; second, 0.30 cc.; third, 0.35 cc.; fourth, 0.40 cc.; fifth, 0.45 cc.; sixth, 0.50 cc.; seventh, 0.55 cc.; eighth, 0.60 cc.; ninth, 0.65 cc.; tenth, 0.70 cc.; eleventh, 0.75 cc.; twelfth, 0.80 cc.; thirteenth, 0.85 cc.; fourteenth, 0.90 cc.; fifteenth, 0.95 cc.; sixteenth, 1.00 cc.; seventeenth, 1.00 cc.; eighteenth, 1.00 cc.; nineteenth, 1.00 cc.; twentieth, 1.00 cc.

If, at any time, the patient notices slight flushing of the face or any other symptoms indicating subjective or objective response to the drug, the next dose should be reduced 50 per cent. An attempt then is made gradually to increase the dose again.

These increasing subcutaneous injections are administered twice daily for approximately ten days to three weeks. After the patient is free from attacks, the second phase of the problem is to prevent future attacks. This can best be accomplished by giving each patient a proper maintenance dosage. This will consist in giving the patient approximately 1 cc. of histamine diphosphate (0.275 mg. of histamine diphosphate) one to three times weekly. The average patient will probably require two injections weekly, whereas a few patients apparently do not require a maintenance dose.<sup>16</sup>

The several conditions discussed make up the bulk of cases of headache that one sees in medical practice. It is acknowledged that there will be many cases that do not fit into any of the above groups, but if one tries to properly classify each case, his therapeutic task will be greatly simplified. Once the diagnosis is made, let us approach the problem of treatment with increasing optimism and we shall be rewarded by encouraging results.

## BIBLIOGRAPHY

1. Woltman, H. W.: The symptoms of headache and some conditions suggested by it, *Minn. Med.*, 23:19 (Jan.) 1940.
2. Morrison, W. W.: *Diseases of the Nose, Throat and Ear*, Philadelphia, Saunders, 1938.
3. Williams, H. L.: The syndrome of physical or intrinsic allergy of the head. II. Ménière's disease (endolymphatic hydrops), *Proc. Staff Meet. Mayo Clin.*, 20: 373 (Oct. 17) 1945.
4. ———: The use of benadryl in physical allergy of the head, *Proc. Staff Meet. Mayo Clin.*, 20:417-438, 1945.
5. ———: The syndrome of physical or intrinsic allergy of the head; myalgia of the head (sinus headache), *Proc. Staff Meet. Mayo Clin.*, 20:177 (June 13) 1945.
6. Rose, B.: The relation of histamine to anaphylaxis and allergy, *McGill M. J.*, 10:5-28 (Dec.) 1940.
7. Weiss, E., and O. S. English: *Psychosomatic Medicine*, Philadelphia, Saunders, 1943, p. 450.
8. Alvarez, W. C.: *Proc. Staff Meet. Mayo Clin.*, 14:173 (Mar. 15) 1939.
9. Horton, B. T., G. A. Peters, and L. S. Blumenthal: A new product in the treatment of migraine, *Proc. Cent. Soc. Clin. Research*, 15:91 (Nov. 6) 1942. A new product in the treatment of migraine: a preliminary report, *Proc. Staff Meet. Mayo Clin.*, 20:241 (July 11) 1945.
10. Blumenthal, L. S.: Migraine headache: treatment of fifty-one patients with dihydroergotamine, *Med. Ann. Dist. Columbia*, (Jan.) 1947.
11. Blumenthal, L. S., and M. H. Rosenberg: Benadryl: results of therapy in one hundred forty patients with varied medical conditions. (To be published.)
12. Hines, E. A., and L. M. Eaton: Potassium thiocyanate in the treatment of migraine: a preliminary report, *Proc. Staff Meet. Mayo Clin.*, 17:254 (Apr. 22) 1942.
13. Hines, E. A., and L. M. Eaton: Treatment of migraine with potassium thiocyanate, *J. A. M. A.*, 121:1307, 1943.
14. Atkinson, M.: Use of nicotinic acid as vasodilator in Ménière syndrome and migraine, *Ann. Int. Med.*, 18: 797 (May) 1943.
15. Butler, S., and W. Thomas: Intravenous histamine in the treatment of migraine, *J. A. M. A.*, 128:173 (May 19) 1945.
16. Horton, B. T.: The use of histamine in the treatment of specific types of headaches, *J. A. M. A.*, 116:377 (Feb. 1) 1941.
17. Horton, B. T.: Personal communication.

Rheumatic fever is the leading cause of heart disease from about 5 to 40. . . . High blood pressure is relatively most important in the 40's and 50's. . . . In older persons the predominant cause is arteriosclerosis, usually associated with hypertension. . . . Cardiovascular syphilis is at its peak between 40 and 50. . .

—*Studies in Heart Disease*, p. 12, Metropolitan Life Insurance Company, 1946.

# A Review of the Rh Factor and Its Clinical Significance

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The Rh factor was first demonstrated by Landsteiner and Weiner in 1940.<sup>1</sup> It was called Rh because the factor was originally described in the Rhesus monkey as an antigen present in the erythrocytes. The first two letters of this generic name were used to demonstrate this antigenic substance. The Rh factor has been shown to be present in 85 per cent of the Caucasian race and absent in 15 per cent.<sup>2</sup> In Negroes the incidence of Rh positiveness is 92 per cent and it is 99 per cent in Oriental races.<sup>3-5</sup>

The author does not claim originality for this paper but he believes that the following facts should be recapitulated.

The Rh factor is inherited as a simple dominant Mendelian characteristic as a pair of contrasting genes, and it is not sex-linked.<sup>6-7</sup> The genetic characteristics of an individual may be homozygous (RhRh) (both parents Rh positive), heterozygous (Rhrh) (one parent positive, the other negative), or negative (rhrh) (both negative). The problem as to whether a child born of an Rh positive father and Rh negative mother will always be positive depends upon the genotype of the father, and will follow Mendelian principles of heredity.

It is thought that the Rh antigen is present only in the red blood cells. There is, however, some evidence that Rh factors are present in the plasma.<sup>8</sup> Rh immune bodies occur as the result of sensitization to antigen stimulation. This sensitization may occur as a result of simple whole blood transfusions of Rh positive blood of otherwise matching type into an Rh negative individual; and by multiple pregnancies in an Rh negative woman with a Rh positive husband.

In the discussion of immunologic concepts, including the Rh factor, it is necessary, for the sake of brevity, to utilize certain terms which are arbitrarily set-up, and which convey specific meanings. To facilitate their understanding a brief summary is given below.

In all immunologic reactions there must first be a substance which is capable of producing, in a susceptible individual, a degree of sensitization. This sensitizing substance is called the antigen. The antigen may be of external origin and it may gain access to the body by oral ingestion, injection, or by direct contact with an absorbable surface. In addition, the body itself, through faulty digestive breakdown of varied substances, may produce antigenic substances

which are absorbable.<sup>9</sup> As a rule, a properly functioning liver will destroy or denature many of these substances. In the Rh scheme, the antigen, for the most part, is contained within the erythrocyte; these are called Rh positive erythrocytes. This antigenic substance stimulates, in susceptible (Rh negative) individuals, the production of anti-antigen material, or antibodies, which exist in the circulating blood plasma, and in some cells. The anti-Rh positive antibody produces agglutination of the Rh positive erythrocytes in vitro, and hemolysis in vivo.<sup>10</sup> Therefore the antigenic substance may be designated as an agglutino-gen and the anti-Rh factor, or antibody, as the agglutinin; or as hemolysinogen, and hemolysin, respectively.

In the Rh system, a person who is Rh positive may sensitize an Rh negative individual in the methods discussed below. In this manner, an Rh factor is the antigenic substance which sensitizes a susceptible individual (Rh negative) and produces in the latter anti-Rh positive substances or Rh positive antibodies. The destruction of red blood cells in the affected individual may produce an anemia, extra-medullary erythropoiesis, and the presence of normoblasts in the peripheral circulating blood. Jaundice may result from the increased hemolysis.

The Rh factor has been said to be the cause of intragroup transfusion reactions, the sequence of events being as follows: An Rh negative individual is transfused with Rh positive blood, and there is no detectable effect although anti-Rh positive antibodies are being developed. If a subsequent transfusion of Rh positive blood is given, a hemolytic reaction is likely to occur. As with intergroup transfusion reactions, the severity appears to depend primarily upon the isoagglutination titer of the recipient's plasma and on the quantity of antigenic materials transfused, and upon the unpredictable capacity of the body to handle and throw off the reaction products.

The frequency of reaction from all sources is less in practice than the frequency expected from the sensitization by transfusions. Possible explanations are:

1. Variable Rh antigen potency.
2. Variable capacity to produce Rh isoagglutinins.
3. Variations in the specificity of the Rh factor.

In addition a period of time is required for the

development of Rh isoagglutinin titers and the agglutinins tend to decrease and disappear with time. This time is variable and may extend for several years. It is also possible that some transfusion reactions which have been classified as mild, moderate, or nonspecific reactions in typing and cross-matching may be ascribed to this specific source.

Another manner by which an Rh negative person (female) may become sensitized is by her carrying in utero an Rh positive fetus. It is believed that the Rh positive agglutinogens traverse the placental barriers and sensitize the mother. This may produce two difficulties inasmuch as the anti-Rh positive antibodies (agglutinins) thus formed, may return to the fetus and produce hemolysis of the fetal blood cells. This is called, generically, erythroblastosis fetalis. A sufficient isoagglutinin titer may be produced in the mother so as to give an intragroup specific reaction at the first transfusion given her with Rh positive blood. If the sensitized mother is transfused with blood of the same blood group but not distinguished as to Rh character, the theoretical chances of a reaction are 6 in 7, and would be the same for each subsequent transfusion. Sensitization of the mother occurs with the first child; however, this child may be normal; the second and succeeding offspring will be affected. The incidence of hemolytic disease of the newborn is one in 150–200 births.<sup>11</sup>

Because of the relative chance of occurrence of an Rh positive fetus in an Rh negative mother, and because the degree of sensitization cannot be predicted, Weiner, as a precaution suggests the routine employment of only Rh negative blood of an homologous type for postpartum transfusions. If Rh negative blood is not available, donors with compatible blood are selected on the basis of direct cross-matching at refrigerator, room, and body temperatures using sensitive centrifuge technics.<sup>12</sup>

Antigenic transmission in pregnancy is believed to occur in greatest amount during the second stage of labor, at which time placental tears occur and opportunity is provided for the passage, from the fetus, of erythrocyte-laden villi into the maternal blood. Small breaks or injuries at the placental site during the course of pregnancy might similarly provide the opportunity for passage of the Rh antigen into the maternal circulation.<sup>13</sup> It has been thought that high doses of vitamin C given to Rh negative females with Rh positive husbands may abort the consequences of Rh sensitization by decreasing the permeability of the placental villi. No conclusions have been drawn.<sup>14</sup>

Once a woman is sensitized there is no active way to desensitize her. Repeated phlebotomy with re-

peated transfusions with homologous Rh negative blood have been undertaken, but no definite conclusions have been reached. A method similar to this has been suggested for the treatment of erythroblastotic babies. The injection of typhoid vaccine into Rh negative pregnant women to diminish or forestall the production of Rh sensitivity has been performed on the premise that if one susceptible individual is simultaneously exposed to two antigens, the antigens compete with each other. Typhoid vaccine produces antibodies more easily than the Rh factor.<sup>14</sup> This work is still in the experimental stage.

Ordinary agglutination tests and cross-matching do not reveal Rh incompatibility. In the absence of immediately available sera for specific Rh tests these Rh reactions can be prevented by subjecting the cross-matching to the warm agglutination test; i.e., the donor's cell suspension and the patient's serum should be incubated for 30 minutes at 37° C. Any Rh negative patient who must receive repeated transfusions over a period of time should be protected from possible isoimmunization, which may result from being given blood from Rh positive donors.

Chown and Lewis have devised a simplified method for blood cell typing which can be used at the bedside or in the office in a short period of time.<sup>15</sup> This test is based upon macroscopic clumping and blood taken for routine Wassermann tests is suitable.

The test requires small amounts of serum and is based on an agglutination reaction. When capillary tubes of 0.4 mm. bore containing a mixture of erythrocytes in suspension and agglutinating serum are set at an angle of 45 degrees, the Rh positive cells form clumps which are visible to the naked eye. Rh negative cells do not exhibit this tendency. The test is accurate for titration of agglutinins in a titer greater than 1:4.

The method is as follows:

	USING CLOTTED OR CITRATED BLOOD (blood drawn for Wassermann is suitable).	USING DROP OF CITRATED BLOOD FROM FRESH PUNCTURE (patient or donor).
Step:		
1.	Place 0.25–1.0 cc. of blood in a small test tube and add about 5.0 cc. of 0.85% saline solution.	Dip tip of capillary in anti-Rh serum. Let 0.5–1.0 inch run in. Lay on desk.
2.	Centrifuge	Puncture skin. Express a small drop of blood.
3.	Pour off saline. Shake! (this produces a 25%–50% suspension).	Place a drop of 3.8% citrate solution beside it.
4.	Dip the tip of a standard capillary tube in anti-Rh serum. Let 0.5–1.0 inch run in.	Mix with stem of capillary tube.

5. Dip serum filled end of capillary tube into blood cell suspension, and let 0.25–0.5 inch run in. Same as No. 5 in column I.
6. Invert capillary tube and center the blood column. Place at a 45° angle in front of a lighted viewing box.

The test cannot be done with undiluted serum or plasma as these may produce a false agglutination. The coagulation tubes found to be most suitable are 9.5 cm. long and 0.4 mm. in diameter.

A positive reaction produces a string-of-beads or clumping appearance; Rh negative cells form a smooth ribbon. The reactions are rapid, and the authors state that at room temperature with good serum most reactions are visible in five minutes. Chown and Lewis do not read any test as negative until 30 minutes have elapsed. A magnifying glass may be used to facilitate the reading of test reactions and to determine early and doubtful reactions. The speed of the reaction varies directly with the titer of the serum.

Errors in technic may occur from:

1. Using too strong blood sera which may yield false + reactions.
2. Weak sera.
3. Old or contaminated cells.
4. Too little blood volume which may prohibit clumping.
5. Biologic error due to the presence of blocking antibodies which may prevent the agglutination of Rh + cells by anti-Rh + serum.

For a further description of the technics of the Rh agglutination test and the detection of anti-Rh factors in human serum the reader is referred to the bibliography.<sup>16-17</sup>

In the treatment of erythroblastosis and minor degrees of congenital anemia it is preferable to use Rh negative blood rather than Rh positive as Rh positive agglutinins which might still be present in the baby's serum would hemolyze the Rh positive cells given by transfusion. The baby should not receive blood from the mother as the mother's sera contains Rh positive agglutinins. In addition the mother should not nurse the baby as the milk also contains agglutinins.<sup>12</sup>

Subgroups of the Rh factor designated as Rh<sub>1</sub>,<sub>2</sub> etc., and Hr have been discovered.<sup>18</sup> In addition blocking antibodies, or antibodies which react only under certain conditions, and are univalent as differentiated from the bivalent type demonstrable by ordinary technics are described.<sup>19</sup> Weiner has developed the conglutination test as a means of detecting Rh sensitization which requires a third substance similar to complement.<sup>20</sup>

It may thus be seen that knowledge of the Rh factor and its significance is essential for the practice of good medicine and the ultimate welfare of the patient.

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## BIBLIOGRAPHY

1. Landsteiner, K., and A. S. Weiner: An agglutinable factor in human blood recognized by immune sera for rhesus blood, *Proc. Soc. Exper. Biol. & Med.*, 43:223 (Jan.) 1940.
2. Weiner, A. S.: The Rh blood types and some of their applications, *Am. J. Clin. Path.*, 15:106–121 (Mar.) 1945.
3. Weiner, A. S., R. B. Belkin, and E. B. Sonn: Distribution of A<sub>1</sub>, A<sub>2</sub>, B, O, MN and Rh blood factors among negroes in New York City, *Am. J. Phys. Anthropol.*, 2:187–194 (June) 1944.
4. Levine, P., and H. Wong: The incidence of Rh factor and erythroblastosis fetalis in Chinese, *Am. J. Obst. & Gynec.*, 45:832–835 (May) 1945.
5. Weiner, A. S., et al.: Distribution of heredity and human blood properties, A, B, M, W, P, and Rh (in Asiatic Indians), *J. Immunol.*, 51:227–230 (Oct.) 1945.
6. Weiner, A. S., et al.: Heredity of the Rh factor, *Genetics*, 28:157, 1943.
7. Race, R., et al.: Rh gene; inheritance of allelomorph in 56 families, *Ann. Eugenics*, 12:206–210 (Oct.) 1944.
8. Boorman, K. E., and B. E. Dodd: The group specific substances, A, B, M, N, and Rh: their occurrence in tissues and body fluids, *J. Path. & Bact.*, 55:329–339 (July) 1943.
9. Boyd, W.: *Text-Book of Pathology*, Philadelphia, Lea & Febiger, 3rd ed., 1938, p. 571.
10. Sinclair, F. D.: Transfusion accidents and isoimmunization, *J. Oklahoma M. A.*, 35:288 (July) 1942.
11. Diamond, L. K.: The clinical importance of Rh blood types, *New England J. Med.*, 32:447–450; 475–480 (April) 1945.
12. *Lectures in Internal Medicine*, Cook County Graduate School of Medicine, Chicago, April 1946.
13. *Lectures in Pathology*, Cook County Graduate School of Medicine, Chicago, October 1946.
14. Unger, L. S.: The Rh factor, *Am. J. Nursing*, 45:688–690 (Sept.) 1945.
15. Chown, B., and M. Lewis: Further experience with the slanted capillary method for Rh typing of red blood cells, *Canad. Med. A. J.*, 55:66–69 (July) 1946.
16. Diamond, L. K., and N. M. Abelson: Rh sensitization; detection and evaluation of tests for Rh antibodies, *J. Lab. & Clin. Med.*, 30:668–674 (Aug.) 1945.
17. Ritmiller, L. F., et al.: Rh test; use and practical applications, *Pennsylvania M. J.*, 48:897–899 (June) 1945.
18. Levine, P.: Hr factor and Rh genetic theory, *Science*, 102:1–4 (June) 1945.
19. Weiner, A. S.: Conglutination test for Rh sensitization, *J. Lab. & Clin. Med.*, 30:662–667 (Aug.) 1945.
20. Weiner, A. S.: A new test (blocking test) for Rh sensitization, *Proc. Soc. Exper. Biol. & Med.*, 56:173–176 (June) 1944.

*Great strides have been made in recent years in the chemotherapy of malaria. The author compares the new drugs with the older ones such as atabrine and quinine.*

## New Knowledge in the Treatment of Malaria\*

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Problems relating to the diagnosis, treatment, and prophylaxis of malaria occupied a place of outstanding importance during World War II. The situation of having to transport millions of Americans, most of whom had never had malaria, to war areas where malaria was hyperendemic, together with the loss of the source of supply of what was then considered to be the most effective drug, quinine, posed a challenge whose outcome could well have determined the success of the conflict in certain areas.

This situation resulted in a concentration of energies and resources upon this problem on a scale heretofore unknown for any disease. Military and civilian research organizations collaborated closely under a Board for the Co-ordination of Malaria Studies, which integrated the widespread activities carried on in the fields of synthesis, pharmacology, toxicology, and clinical testing of antimalarial drugs. Approximately 14,000 drugs were tested for their antimalarial activity during the course of this research. As a result of this intensive research program it was possible to learn in months what would ordinarily have taken years. The disaster of losing the source of quinine was eventually turned into a benefit to mankind, for drugs have been discovered which far surpass quinine in antimalarial effect. Furthermore, techniques for assaying the effects of antimalarial drugs have been placed upon so secure a foundation that it is a comparatively simple matter now to evaluate any new drug which appears upon the scene. The information obtained by the newer methods of evaluation, as they apply to previously known and to new drugs, provide a more rational basis for the therapy of malaria than has hitherto been available, and will serve as a basis for discussion here. Problems relating to the therapy of vivax and falciparum infections only will be considered, since malarial infection due to *Plasmodium malariae* does not constitute an important problem in this country, and responds in general

to chemotherapy which is effective against the other two species.

In any consideration of the treatment of malaria it is necessary to take into account the different morphologic stages of the malaria parasite which may exist in man, their relationship to the production of symptoms, and the extent to which these stages may be influenced by drugs. No known drug acts with equal effectiveness upon all these stages. Drugs which are highly effective upon one stage of the parasite may be completely ineffective upon other stages. Unfortunately, some of the stages which are resistant to therapy play an important role in symptomatology. Furthermore, certain drugs are more effective in one species than in another; for example, the arsenical drugs act upon vivax malaria, but not upon falciparum malaria, while sulfonamide drugs are more effective in falciparum than in vivax malaria. Also, different strains of the same species of malaria may show considerable variation with regard to the amount of a specific drug required for effective chemotherapy. These factors complicate drug therapy of the malarias and necessitate a clear understanding of the cycle of malaria in the human host and of the stage in the cycle affected by a particular drug. First consideration will therefore be given to the action of drugs upon the three stages of the parasite which are believed to exist in man; namely, the sporozoites, the intermediate tissue forms, and the erythrocytic forms found in the blood.

### THE SPOROZOITES

This stage of the parasite is injected by the infected mosquito into man. No symptoms are produced by these forms; in fact, none are evident for approximately ten days or more subsequent to infection. A drug which would be effective in destroying these forms would be considered as a true "prophylactic" and would represent the ideal drug from many standpoints. Unfortunately, there is only one drug which has given any suggestion of being effective against this stage of the cycle; namely, plasmochin (pamaquine U.S.P.). James,<sup>1</sup> in studies carried out in England

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about 15 years ago, showed that the administration of plasmochin for eight days in high dosage, beginning the day before mosquito inoculation, would prevent vivax and falciparum infections from developing in 100 per cent of cases. This work subsequently received little attention until World War II, when an attempt was made by research groups in the United States to re-evaluate this drug in the hope of obtaining a lead for further investigations in the field of prophylactic drugs. As a result of these studies, the work of James was confirmed and elaborated upon.<sup>2</sup> It was observed that plasmochin, in dosage comparable to that employed by James, acted as a prophylactic of falciparum infections and prevented the primary attack of vivax malaria, although it failed to prevent subsequent clinical activity, six to eight months later, of the latter species. While it was not possible to decide unequivocally which stage of the parasite was affected by plasmochin, the impression was gained that the effect was not upon the sporozoite stage but upon a subsequent stage of development of the parasite in the tissues. This evidence that plasmochin possessed a type of activity not possessed by any other known antimalarial drug, together with increased knowledge of the nature of its toxicity for man, led to further search for analogs of this drug which might have similar activity but less toxicity. The results of this research will be discussed later.

### THE INTERMEDIATE TISSUE FORMS

These represent the stages into which sporozoites develop, and from which the erythrocytic blood forms which produce symptoms arise. Such tissue forms have never been demonstrated in man, but have been demonstrated by James and Tate<sup>3</sup> in bird malaria, and it is presumed that they also exist in man, as no erythrocytic forms can be demonstrated for at least seven to nine days after the injection of sporozoites, and sub-inoculations of blood are not successful during this period. These forms have been referred to as "cryptozoites" or "exoerythrocytic" forms. They are believed to be responsible for the relapses which occur in vivax infections. The latter represent one of the most important problems of present-day malaria in men returning from the Southwest Pacific, as the species of vivax malaria acquired there is notorious for its frequency of relapses. These occur at short intervals and are not prevented by any commonly used regimen of treatment.

As a result of this problem, and of the renewed interest in plasmochin resulting from the studies mentioned above, a reinvestigation was made of work carried out by Sinton and Bird<sup>4</sup> in 1928, in which it was

claimed that a combination of plasmochin and quinine given for three to four weeks reduced the relapses of vivax malaria to a marked degree. The outcome of these recent studies has been to show that when quinine (2 Gm. daily) and plasmochin (90 mg. of base daily) are given concurrently for 14 days, the relapses of vivax infections (Southwest Pacific strains) are reduced to a minimum.<sup>5</sup> This is heroic treatment and requires hospitalization. Adequate supervision and an understanding of the toxic symptoms which may be encountered are essential for safety.

Recently a new drug has been developed, which has a chemical structure similar to that of plasmochin, but is approximately half as toxic in man. This drug, which was number 13,276 on the list of drugs studied, has been named pentaquine.<sup>6</sup> Given over a period of two weeks in daily dosage of 60 mg. base, combined with 2 Gm. quinine daily it will eradicate the relapses of vivax malaria in a manner comparable to when 90 mg. of plasmochin is employed. While the toxicity of this new drug is less than that of plasmochin, it is by no means inconsiderable, and patients receiving this drug should preferably be hospitalized. An alternative method, less hazardous to the patient, for dealing with the relapses of vivax malaria will be discussed later.

Attention should be called at this point to the increase in toxicity which results when plasmochin is administered concurrently with atabrine. This is the result of a peculiar "potentiating" action atabrine has upon plasmochin producing a blood concentration of the latter drug which is many times that observed when plasmochin is given alone.<sup>7</sup> For example, in a series of patients who were given 30 mg. of plasmochin base daily, the mean plasma concentration of plasmochin was approximately 30 micrograms per liter. When, to the same amount of plasmochin, 0.3 Gm. of atabrine was added daily, the plasma concentration of plasmochin reached an average level of 300 micrograms per liter, with a proportional increase in toxic manifestations. This explains the toxic manifestations observed during the early World War II Army regimen of treatment which employed plasmochin as terminal treatment following the administration of quinine and atabrine. Due to its slow excretion, atabrine still remained at a significant plasma level after its administration was discontinued, and exerted the potentiating action described above.

### THE ERYTHROCYTIC BLOOD FORMS

The term "suppression" is now being applied to any effect upon these erythrocytic forms, whether it be in terminating the acute clinical attack or in pre-

venting clinical manifestations by periodic administration of a drug in anticipation of infection. For purposes of clarity, the terms *suppression of the clinical attack* and *field-type suppression* will be applied to these respective effects.

**Suppression of the Clinical Attack.** For purposes of chronologic reference, one might refer to three eras of drug therapy, the quinine era, the atabrine era, and the present (and future) era of new drugs, such as the 4-aminoquinolines and paludrine. The supremacy which quinine enjoyed in the field of malaria therapy endured well into World War II. This is the strongest tribute which can be given to this drug, in view of the fact that atabrine had already been upon the scene for ten years, and the League of Nations Commission as long ago at 1933 had stated that in spite of the widespread use of cinchona alkaloids for over 300 years, there was no consensus as to optimum dosage and mode of action.<sup>8</sup> As will be pointed out later, persistence in the use of quinine after the introduction of atabrine was due to lack of understanding of the proper use of the latter drug rather than to any inherent superiority of quinine.

The conflicting reports regarding the optimum dosage of quinine, and the regimen of choice, which fill the literature of the past, are due to the empirical methods of treatment formerly employed. One of the important contributions of the wartime malaria research program has been to replace these empirical methods of the past by a more quantitative approach, relating the antimalarial activity of drugs to their concentration in the blood rather than to oral dosage. This represents an attempt to apply to malaria the same type of quantitative approach which permitted of sound antibacterial therapy with the sulfonamide drugs.

In studies carried out upon quinine early in the war, an attempt was made to determine the minimum plasma concentration which would produce a remission of parasites and fever. Plasma concentrations of 5 mg. per liter were needed to produce such an effect upon the strain of vivax (McCoy) employed. This level could usually be achieved by the administration of from 15 to 20 mg. per kilogram of body weight, or approximately 1.0 to 1.5 Gm. daily to a 70 Kg. patient. However, considerable variation was encountered in the plasma levels achieved in different individuals receiving the same dose of drug. For example, in a group of patients receiving 0.3 Gm. of quinine daily, the mean plasma concentration varied from 2 to 8.9 mg. per liter.<sup>9</sup> This indicates the hazard of relating antimalarial effect solely to oral dosage. Some strains of vivax malaria require more quinine for control

than do others, while falciparum strains in general require a higher plasma concentration for control than is required by vivax malaria. A safer minimum dosage to employ would therefore be 2 Gm. daily for vivax infections and 3 Gm. daily for falciparum infections, with checking of plasma concentrations to insure that an adequate level is being achieved.

Quinine is rapidly absorbed, but is also rapidly degraded and excreted, so that a rapid fall in plasma concentration occurs when dosage is discontinued. Therein lies its main inferiority to drugs like atabrine, which as a result of tissue localization and slow degradation and excretion maintain blood concentrations high enough to affect erythrocytic forms for considerable periods of time following administration. Negligible quantities of quinine can be detected in the plasma 24 hours after administration, whereas evidence of atabrine may be detected for weeks or even months. The advantages of the latter drug from a suppressive standpoint are evident.

The loss of the source of supply of quinine from the Dutch East Indies early in the war made observations on quinine of academic rather than practical interest, although quinine continued to be used as a standard for the evaluation of other antimalarial drugs. In the summer and fall of 1942 there appeared to be no suitable drug available in amounts sufficient to conduct large scale military operations in hyperendemic areas. Atabrine was the only drug available, but was in low repute as a result of reports coming in from the services regarding its shortcomings. Since it was the only drug available, however, the Board for the Co-ordination of Malarial Studies decided to reinvestigate this drug so that it might be used to best advantage. Prior to this time, atabrine had not even been completely synthesized in this country, but had been sent here in partially synthesized form from Germany, so that a problem of complete synthesis as well as evaluation presented itself. The results of the studies which were undertaken probably contributed as much to the success of the campaign in the Southwest Pacific as any other single factor. Men ill with malaria cannot engage in combat. The proper use of atabrine in the suppression of malaria was so effective, once its potentialities were realized, that the disease was reduced from a "number one" problem to a minor one. Certain aspects of the research which produced this striking change in the picture deserve mention here.

As in the case of quinine studies, an attempt was made to relate the antimalarial activity of atabrine to the concentration of this drug in plasma. Fortunately a method for doing this was developed by



Brodie<sup>10</sup> in 1943 and applied to this problem. It was thus possible to determine the relationship of oral dosage and other routes of administration to plasma concentrations, and of plasma concentrations to antimalarial effect. As has been pointed out by Shannon,<sup>11</sup> the plasma concentration of atabrine depends upon the dosage employed, the route of administration, and the operation of the processes of absorption, distribution, degradation, and excretion. Studies of the distribution of atabrine revealed why previous regimens of therapy had proved so inadequate. A major portion of administered atabrine is at first localized in tissues and organs of the body, leaving little in the plasma to exert a therapeutic effect. The dosage formerly employed, 0.1 Gm. three times a day, was found to be inadequate, as most of the early medication localized in the tissues and produced no effect upon the erythrocytic forms which produce symptoms. For example, in the case of standardized strains of vivax and falciparum malaria employed in evaluation studies in this country, it was observed that the minimum effective plasma concentrations of atabrine required for the control of these infections were 30 and 50 micrograms per liter, respectively. When the above regimen of treatment was employed in a series of test patients, the minimum plasma concentration effective against vivax malaria was not reached until the second day of treatment, whereas that required for falciparum malaria was not reached until the fifth day. This explains the poor results achieved with such dosage, particularly in falciparum infections. For this reason large initial doses ("priming doses") must be given, preferably 0.2 Gm. every six hours for five doses, followed by 0.1 Gm. three times a day for six days. Extremely high plasma concentrations can be achieved by intramuscular administration of 0.2 Gm. in each buttock; this produces a plasma concentration of over 100 micrograms per liter within fifteen minutes. This is the method of choice in treating comatose cases or those who cannot tolerate the drug by mouth due to vomiting. This method should replace the older procedure of giving quinine intravenously, as the latter is associated with great risk, and possesses no advantages.

This knowledge of the potentialities of atabrine must be tempered, however, by a recognition of certain toxic properties of this drug. The yellow staining of the skin is well known. Gastro-intestinal irritation may occur, especially if the drug is given before meals. In certain predisposed individuals, cerebral irritation may occur which may reach the proportions of a psychosis. In patients with organic brain deterioration due to syphilis who are being treated with

malaria, the incidence of convulsive seizures is higher when atabrine is used than when other drugs are employed for terminating the malaria.<sup>12</sup> Dermatologic manifestations taking the form of an atypical lichen planus have also been reported in troops under field-type suppression.<sup>14</sup> These toxic effects indicate that even atabrine has its drawbacks, and is not the ideal drug one might wish for.

Fortunately, new drugs have appeared upon the horizon as a result of the intensive wartime research program, and it is quite conceivable that within a few years atabrine will become an obsolete drug. In this country the most promising of the newer drugs are the members of the 4-aminoquinoline series. One of these, chloroquine<sup>15</sup> (aralen) (SN 7618) will probably be widely used in the future.

When the rate of disappearance of parasites from the blood stream under the influence of quinine, atabrine, and chloroquine is compared, it is observed that quinine runs a poor third, trailing atabrine by 24 hours in clearance results, whereas chloroquine is superior to atabrine in parasite clearance and is effective in shorter courses of treatment. A recommended course of treatment with chloroquine consists of 2.5 Gm. of diphosphate given over a period of three days, as follows:

First day.	8 A.M.	1.0 Gm.
	4 P.M.	0.5 Gm.
Second day.	8 A.M.	0.5 Gm.
Third day.	8 A.M.	0.5 Gm.
		—
Total		2.5 Gm.

Similar total dosage divided over a 24-hour period has also been employed without significant toxic manifestations. As in the case of atabrine, a priming dose should be administered initially, in order to achieve a high plasma concentration rapidly.

Chloroquine does not produce the staining of the skin which atabrine produces. It is well tolerated during the acute attack and controls symptoms so promptly that patients who have taken other anti-malarials such as quinine or atabrine prefer the new drug. Patients who cannot tolerate atabrine will usually tolerate chloroquine well. Toxic symptoms occur less frequently than with atabrine. Of these the commonest are mild and transient headache, pruritis, gastro-intestinal symptoms, and blurring of vision.

Chloroquine is similar to atabrine in that it does not prevent the relapses of vivax malaria. However, the interval between relapses is longer and the number of relapses fewer than when quinine or atabrine

are employed. Chloroquine suppresses the acute attack and completely cures falciparum infections. The effective plasma concentration for chloroquine is considerably less than that required for atabrine, and in standardized infections it is approximately three times as active as atabrine.

Another product of wartime malaria research is a British drug named paludrine.<sup>16</sup> This drug is of interest in that it has a chemical structure entirely different from that of the other drugs mentioned above. Of particular interest is the claim made by British investigators that this drug acts as a true prophylactic against falciparum malaria and is also effective against the gametocytes of this species. One of the shortcomings of drugs employed in the past, such as quinine and atabrine, is that while they control the clinical symptoms of falciparum malaria adequately, they do not affect the gametocytes of this species, and therefore the patient continues to be infectious to mosquitoes. On our research service we have been able to infect mosquitoes from such patients for weeks after the completion of a full course of atabrine, and during periods when the patient was completely free of fever or symptoms of malaria. The propagation of malaria is favored by such circumstances. Paludrine therefore appears to be unique in this property of being highly active against the sexual as well as asexual forms of falciparum malaria, a property not possessed by any other known drug. A partial prophylactic effect against vivax infections is also claimed for this drug.

Furthermore, the difference between the effective therapeutic dose and the toxic dose of paludrine is much greater than for any other known drug, thus providing a considerable margin of safety. In some respects paludrine appears to be slightly inferior to chloroquine, namely, in the speed with which the blood stream is cleared of malaria parasites and in the duration of treatment required for such clearance. Whether these deficiencies can be overcome or whether they are of serious significance will be determined by further studies. Such studies are being carried out in various parts of the world to determine the place which this drug shall occupy among our anti-malarial weapons. Even if paludrine turns out to be the most potent drug we possess, as claimed by British workers, it still fails in one respect to achieve the status of the ideal antimalarial drug, namely, in its failure to prevent the relapses of vivax malaria.

**Field-Type Suppression.** What has been said with regard to suppression of the clinical attack also applies to field-type suppression. In field-type suppression, as in the suppression of the acute clinical attack,

chloroquine and paludrine will undoubtedly supplant atabrine. The latter drugs have the advantage over atabrine in that they are effective when given once a week, whereas atabrine must be given almost daily.<sup>17</sup> The absence of the yellow staining of the skin produced by long periods of administration of atabrine is also in favor of the newer drugs. We have been particularly interested, during the past year in determining the minimum amounts of the newer drugs which will suppress our strains of vivax and falciparum infections. In our experiments we allow heavily infected mosquitoes to feed on patients on three alternate days during the first week of observation, to simulate natural infection in a hyperendemic area. Patients receive a single dose of drug weekly, starting the day before the first mosquito inoculation. Preliminary experiments<sup>18</sup> indicate that against the standard vivax infection employed, paludrine was effective in field-type suppression when a weekly dose (0.087 Gm. base) one-third as great as that required in the case of chloroquine (0.25 Gm. base) was employed. Slightly larger dosage of each drug was required against falciparum infections. The effectiveness of paludrine at such low dosage may be of great value in mass suppression in hyperendemic areas, as under such circumstances the toxic manifestations encountered over long periods of administration are of prime importance. Toxic effects have not been reported with the low dosages mentioned. Furthermore, evidence that such small doses affect pre-erythrocytic stages of the parasite even more than erythrocytic forms leads us to predict that paludrine will prove to be the drug of choice in field-type suppression of the future.

While field-type suppression was developed primarily to maintain the efficiency of troops in hyperendemic areas, it may also be applied to troublesome relapsing cases of vivax malaria. During the past year we have observed a number of cases of relapsing vivax malaria acquired in the Southwest Pacific in which repeated clinical activity occurred, sometimes as frequently as two weeks apart, and in which atabrine was either ineffective or could not be tolerated. These men were given one tablet of chloroquine containing 0.25 Gm. of base once a week. Over a period of many months these patients have had no further clinical activity and have been able to accept employment, which had heretofore been impossible. Such a regimen of treatment may be continued for a year or more until the infection burns itself out, as no harm is reported from such prolonged courses of treatment. This form of treatment is a safer alternative to the quinine-plasmochin course mentioned above, which

requires hospitalization and careful observation for at least two weeks.

In conclusion, it is evident that great strides have been made in the field of malaria chemotherapy in recent years under the pressure of the urgent wartime need for knowledge in this field. Even with the passing of the emergency period this knowledge will continue to be a valuable asset to the practicing physician. Physicians will be called upon to treat relapsing vivax malaria acquired in the Southwest Pacific and in the Mediterranean areas for some time to come, in addition to indigenous cases. Of the 60,000 cases of malaria reported in the U. S. A. by State Health Officers in 1945, approximately 20,000 were contracted outside the U. S. A. These latter represent infections acquired during military service for the most part. It has been demonstrated that malarial infections acquired in foreign countries which relapse after return to the U. S. A. are infective to our native American anopheline mosquitoes. Under these circumstances it is conceivable that malaria may again appear in some areas which have been malaria free. In any case it behooves the physician to keep in mind the possibility of malarial infection in those who have recently traveled abroad, and in patients with unexplained fever.

Continued emphasis upon mosquito control as the fundamental malaria control procedure is therefore still needed. Where such control measures break down the physician must be prepared to treat the resulting consequences of malaria transmission with the best drugs available. In this respect he is better equipped than at any previous period in the history of medicine.

#### BIBLIOGRAPHY

1. James, S. P.: The therapeutics of malaria, *Quart. Bull. Health Organ., League of Nations*, 2:197 (June) 1933.
2. Feldman, H. A., Henry Packer, F. D. Murphy, and R. B. Watson: Pamaquine naphthoate as a prophylactic in vivax and falciparum infections, *J. Clin. Investigation*. In press.
3. James, S. P., and P. Tate: Preparations illustrating the recently discovered cycle of avian malaria parasites in reticuloendothelial cells, *Trans. Roy. Soc. Trop. Med. & Hyg.*, 31:4 (Jan.) 1937.
4. Sinton, J. A., and W. Bird: Studies in malaria with special reference to treatment: plasmoquine in treatment of malaria, *Indian J. M. Research*, 16:159, 1928.
5. Berliner, R. W., et al.: Pamaquin: curative antimalarial action in vivax malaria, *Federation Proc.*, 5:165 (Feb.) 1946.
6. Board for the Coordination of Malarial Studies: Activity of a new antimalarial agent, pentaquine (SN 13,276), *J. A. M. A.*, 132:321, 1946.
7. Kennedy, T. J., et al.: A mechanism of drug 'potentiation': pamaquin metabolism as influenced by quinacrine, *Federation Proc.*, 5:185 (Feb.) 1946.
8. Malaria Commission: The therapeutics of malaria, *Quart. Bull. Health Organ., League of Nations*, 2:224 (June) 1933.
9. Taggart, J. T., et al.: Cinchona alkaloids: physiological disposition in man, *Federation Proc.*, 5:206 (Feb.) 1946.
10. Brodie, B. B., and S. Udenfriend: The estimation of atabrine in biological fluids and tissues, *J. Biol. Chem.*, 151:299, 1943.
11. Shannon, J. A., et al.: The pharmacological basis for the rational use of atabrine in the treatment of malaria, *J. Pharmacol. & Exper. Therap.*, 81:307, 1944.
12. Shannon, J. A., and D. P. Earle: Recent advances in the treatment of malaria, *Bull. New York Acad. Med.*, 21:467 (Sept.) 1945.
13. Welch, W. J., et al.: The incidence of convulsions in general paretics receiving quinacrine, *Federation Proc.*, 5:213 (Feb.) 1946.
14. Livingood, C. S., and F. R. Dieuaide: Untoward reactions attributable to atabrine, *J. A. M. A.*, 129:1091 (Dec. 15) 1945.
15. Board for the Coordination of Malarial Studies: Activity of a new antimalarial agent, chloroquine (SN 7618), *J. A. M. A.*, 130:1069 (April) 1946.
16. Fairley, N. H.: Researches on paludrine (M 4888) in malaria, *Trans. Roy. Soc. Trop. Med. & Hyg.*, 40:105 (Oct.) 1946.
17. Fairley, N. H.: Chemotherapeutic suppression and prophylaxis in malaria, *Trans. Roy. Soc. Trop. Med. & Hyg.*, 38:312 (May) 1945.
18. Packer, Henry: Experimental field-type suppression with SN 8137, SN 7618 (chloroquine), and SN 12,837 (paludrine) against vivax and falciparum infections, *J. National Malaria Soc.* In press.

## WHAT'S YOUR DIAGNOSIS?

A 35-year-old phosphate plant employee was admitted to the Medical Service on July 1, 1940 complaining of a "knot" in the upper abdomen. He had always been in exceptionally good health until approximately a year before when he developed epigastric discomfort, nausea, vomiting and cramping abdominal pains. An x-ray at that time revealed the presence of gallstones. There was no associated diar-

rhea, jaundice, or fever. He was sick for about a week but did not return to work for two months.

About eight months before admission he again developed abdominal pain for three days. This was aggravated by food.

About one and one-half months before admission the epigastric discomfort recurred and was severe enough to make him stop work. One month before

he developed severe sharp pain in the left thigh which was accentuated by coughing and sneezing. He then developed pleurisy on the left with fever of 104° F., night sweats, malaise, anorexia and cough productive of thick mucoid sputum but no blood. Two weeks before entry his stools became watery and bowels moved about three times daily. At this time he first noted a tender epigastric mass which increased progressively in size and tenderness. There was some spread of the pain to both flanks. He lost about 20 lb. during this time. These symptoms continued until he was admitted. He vomited several times during the preceding week. No history of jaundice or acholic stools.

His wife died of tuberculosis about seven months before. An x-ray of the patient's chest was negative in September 1939.

**Physical Examination.** Temperature 100.4°; pulse 120; respiration 26; blood pressure 125/75. He was a poorly nourished, pale, moderately ill man of 35. Numerous melanotic areas were scattered over the arms and trunk. Conjunctivae were pale. Pupils and fundi were normal. Ears, nose and mouth were not remarkable except for numerous missing teeth. Thyroid not enlarged. There was retraction of the thorax in the right infraclavicular region. A precordial bulge was noted. The chest expanded equally. A pleural friction rub was felt and heard in the left axilla. There was dullness with diminished breath and voice sounds and diminished tactile fremitus at the left base. Heart was enlarged slightly to the left. Regular in rhythm. No significant murmurs were heard. The epigastrium was bulging with a circumscribed, tender mass which protruded from under the xiphoid process. The center of the mass was fluctuant. The liver edge could be felt beneath the mass 1 or 2 cm. There was definite muscle spasm in the region of the mass. The mass did not descend with respiration. There was evidently some free fluid in the peritoneal cavity. The spleen and kidneys could not be felt. No other masses were felt. Genitalia were normal. Rectal examination was negative except for hemorrhoids. Extremities and reflexes were normal.

#### LABORATORY DATA

**Urine.** Three urine specimens on the first, second, and third hospital days were negative except that the last contained numerous WBC and granular casts.

**Blood.** (2nd Hosp. day) RBC—3.67 millions; WBC—17,000; hemoglobin—9.2 Gm.

Kahn negative.

Nonprotein nitrogen—24.

Blood sugar—93.

Serum cholesterol—115 mg.

Uric acid—2.2.

Icterus index—3.

Total serum protein—6.06.

Stool (1st Hosp. day)—negative.

**X-rays**

2nd Hosp. day Chest: Fluid in left chest. Both sides of diaphragm are elevated but move with respiration.

Plain film of abdomen: Soft tissue mass extending across upper abdomen. Right lobe of liver did not appear to be enlarged.

G-I series: Stomach displaced laterally and the pylorus appeared to be molded around the soft tissue mass. A constant change in the duodenum appeared to be due to external pressure. Marked hypermotility.

3rd Hosp. day Abdomen appeared as previously. On fluoroscopy the heart outline appeared much larger and no pulsations could be seen. There appeared to be some increase in the fluid in the left chest.

**Electrocardiogram:** (2nd Hosp. day) Rate—107, PR—0.12. Low voltage in lead 3—T<sub>3</sub> absent. QRS<sub>3</sub> slurred. ST<sub>1,2</sub> elevated.

(3rd Hosp. day) Above changes became more marked.

**Course:** An irregular high spiking fever and leukocytosis continued until the third hospital day when the patient died. A thoracentesis on July 1 yielded 360 cc. of thin slightly cloudy fluid from the left chest. This fluid was sterile and no organisms were seen on smear. Guinea-pig inoculation was negative. On the same day the epigastric mass was aspirated and 20 cc. thick foul smelling pus was obtained. This yielded an anaerobic streptococcus and a gram-negative bacillus on culture. The patient was then transferred to Surgery where an incision and drainage of the fluctuant area in the epigastrium was carried out. The abscess cavity was not explored. Postoperatively the blood pressure dropped to 90/60 and he perspired profusely. Saline, whole blood and glucose were administered with some improvement temporarily. Dyspnea, râles at both lung bases, tachycardia, pulsus alternans and a paradoxical pulse developed and became marked. Heart sounds remained fairly forceful. He was digitalized and given more blood. Blood pressure remained around 88/68. The venous pressure measured at the end of a transfusion 280 mm. from the level of the heart.

On July 3 a pericardial tap yielded 280 cc. of greenish yellow purulent fluid containing gram-positive cocci in chains. He was then started on sulfanilamide. Respiratory distress continued and 400 cc. fluid was removed from the left chest without relief. He died in shock around 9:30 P.M. on July 3, the third hospital day.

For the diagnosis, please turn to page 574.

*The author reviews the disturbed physiology involved in the gastro-intestinal diseases unassociated with anatomic change. The psychiatric implications are discussed.*

## Functional Derangement of Digestion

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The definition of a functional disorder of the gastro-intestinal tract usually given is that of a condition which is present without any demonstrable lesion elsewhere in the body. This, in my way of thinking, is not strictly true. It is a disorder which does not have a basis of organic pathology, and there may be pathologic conditions elsewhere in the body which have nothing to do with the production of the symptoms in question. It might better be defined as a symptom complex which has no organic basis. After all, to use the criteria that we are unable to find any organic basis, indicates that we do not know what the etiology is. In reality there is no organic basis.

Because most functional disorders are of a relatively minor nature, statistics gathered from hospital admissions do not give a true picture of their relative frequency. I would say, without reservation, that well over 60 per cent of an office practice consists of this type of disorder. The amount of space in most textbooks or reference books that is devoted to functional disorders is indeed relatively small. The situation in this respect is somewhat analogous to that of the common cold. Like the common cold the etiology of these functional disorders is vague, but unlike it the disease is chronic. Treatment is time consuming and does not interest the average busy doctor, who would far rather treat something specific in a definitive manner.

To take up this subject of functional disease in full would require far more space than can be given here. However, if I can leave one thought firmly rooted in your minds, the time is not wasted. This thought is short and concise; namely, that a person with functional disease actually suffers just as much, and sometimes more, than one with organic disease. To the former their symptoms are terribly real. They come to the doctor for relief, not to be told that they are nervous and to forget about the whole thing.

Whether a symptom such as pain is over reacted to, does not lessen its severity to the patient. Because by judicious psychotherapy this pain can be eliminated does not relegate this patient to the realm of those who "imagine their trouble." Because he may have an inadequate personality does not mean that he can be cured with a terse statement. Because he may be under intense nervous strain does not mean that the mere advice to "take it easy" is going to effect a cure. Nor does the knowledge that the basis for his complaints stems from an unfortunate marital status automatically affect a cure when he is so informed.

Roughly speaking there are four etiologic categories into which all gastro-intestinal complaints fall. First there is that group in which there is an actual disease process present in the organ from which the symptoms emanate, this is best illustrated by an active duodenal ulcer. Next there is the symptom complex in which the disease process is removed from the apparent site of the symptoms, as for example pylorospasm associated with chronic appendicitis, or the dyspepsia so often experienced in connection with a diseased gall-bladder. Then there are many systemic diseases which are associated with gastro-intestinal disturbances, and lastly the group of diseases in question, in which there is no pathology present and where the symptoms in some way emanate from the central nervous system.

If we want to be strictly technical all gastro-intestinal symptoms, except true visceral pain, are functional in their origin. By this I mean that an organ's function is disturbed, whether there is an actual lesion in that organ or whether the site of the disturbance is the central nervous system. Vomiting, for instance, is an integrated act, involving reverse peristalsis, dilatation of the cardia, fixation of the diaphragm and contraction of the abdominal muscles. The symptom is the same whether it is due to pyloric obstruction, to the stimulation of the retropharynx with the forefinger, or to the visual image of some disgusting situa-

\* Read as part of postgraduate course sponsored by the American College of Physicians, at Gallenger Hospital, Washington, D. C., on October 24, 1946.

tion. Colicky pain is due to overdistension of a bowel segment due to pressure built up by a descending deep peristaltic wave, working against a point of fixation in the bowel. This point of fixation may be a spasm of neurogenic origin, or it may be an actual occlusion from a circular carcinoma, or a strangulated loop of gut.

For purposes of discussion consider that the entire intestinal tract is a long tube, made up of two layers of muscle fibers and lined with a secreting and absorbing mucosa. Into this are piped the secretions of the liver and pancreas. Running between the muscle layers are two (and according to some observers, five) different nerve plexuses. These plexuses are in turn connected with the autonomic nervous system, which is divided into the sympathetic and parasympathetic, and follows pathways well known to us all. In turn these two systems connect with autonomic centers in the hypothalamus. These centers are influenced by what goes on in the higher centers.

It is well known that the smooth muscle of the gut is autonomous and that it is able to contract rhythmically of its own volition. One of the purposes of the above mentioned nerve plexuses is to integrate these autonomous movements into something purposeful. Intestinal activity is much more than just peristaltic waves passing in a caudal direction. In addition there are segmenting movements in which both ends of a segment of gut constrict and the contents are churned back and forth. There are also rush waves which start periodically and can be traced from the first part of the esophagus to the rectum. Certain swaying movements are noted as well as small reverse wavelets which travel backwards against the larger waves going caudad. Whereas the major portion of the control of these functions lies in the nerve plexuses and ganglion groups, they are under a certain amount of control from the central nervous system. They are affected by conditions of extreme fright, and thus the lower bowel may be emptied automatically. The initiating factor may be a retinal image which is transmitted, interpreted, and correlated in the higher centers, and then the resultant message is transmitted to the various lower centers to prepare the body for a state of defense.

That there is a definite gradient of intestinal activity which normally keeps intestinal contents going in a caudal direction, has been well demonstrated by Alvarez. This gradient is the summation of various other gradients such as contractility, rhythmicity, thickness of muscle, metabolism, chemical activity, etc. This gradient might be likened to a sloping railroad track which begins at a 1,000-foot level and in three

miles is at a 500-foot level. A car placed freely at the top descends at a definitely increasing rate of speed, taking a definite length of time to go from the first point to the second. If there should be a change in the gradient, that is if it is steeper or less sloping, the rate at which the car travels will be increased or decreased. If the center portion only of the track should be raised then the motion of the car is affected, depending upon how much it is raised. If only slightly, then it is only slowed down, if markedly, then the car is stopped, and if raised above the starting point then the car goes backwards. Many organic lesions tend to raise the gradient either entirely or in part, at some point in the intestinal tract. In intestinal obstruction, the symptoms of nausea and vomiting are produced because the gradient at the point of obstruction is raised causing reverse peristalsis, not because the intestinal contents back up against the obstructed point. There may be no actual occlusion of the lumen by an inflammatory mass, yet intestinal contents do not pass, but instead are returned in a cephalic direction. It is not necessary to have an organic lesion to change the gradient. This can be done through the influence of the autonomic and central nervous system. This, I realize, is a very brief description of a most interesting concept. I urge you to read carefully Alvarez' "Introduction to Gastroenterology," which gives the detailed reasoning back of this theory.

For purposes of clarity and simplicity in this discussion we are dealing only with conditions in which there is no organic disease contributing to the etiology. For practical purposes functional disease truly embraces a wider field. For instance, many peptic ulcers have their origin in a psychoneurosis, and are an organic manifestation of a rather profound neurogenic change. A person with a diverticulum may have a rather severe neurosis in conjunction with it, for a diverticulum produces no symptoms as a rule.

So far we have discussed purely motor functions, but it must also be realized that secretory and absorptive activities are under a certain amount of nervous control, either directly or through the medium of hormones. Thus, as a rule, the symptoms associated with functional diseases are the result of a disorder of both the motor and secretory functions of the gastro-intestinal tract. Generally speaking, either the upper or the lower part of the tract is affected, rarely both.

Perhaps the most simple and easily understood functional disorders of the gastro-intestinal tract are those which can roughly be classed as the "habit dyspepsias." It is probably true that they can occur in a

person who is perfectly normal psychologically, but generally speaking they are found in the moderately psychoneurotic, and represent an inability to completely adapt to a situation. The taxi driver who sits in his cab all day, gets no exercise in the accepted sense, eats when the spirit moves him and when he has the time, and consumes an entirely unbalanced diet consisting of coffee and pie, eventually develops dyspepsia usually characterized by constipation, belching, sour eructations, mild epigastric pain and a sense of fullness. He is unhappy and his disposition is bad. He is the one who is nasty and overly abusive when he thinks that another car has cut him off or made him slow up and miss a light. He shows nothing on careful examination, and when he changes his job or takes a true vacation, he feels perfectly all right. Not all taxi drivers suffer this way; many are perfectly adjusted and love their work.

We have all had some contact with the stock broker or the "high-pressure" salesman who works under tension all day and then relives his day's experiences or plans his future strategy during the evening. He never gets away from his work. When you meet him socially his only conversation has to do directly or indirectly with his work. These people frequently have symptoms that in many respects resemble those associated with peptic ulcer; postprandial pain, sour eructations and constipation. There is, however, no seasonal variations to their complaints, and in close questioning if there are exacerbations they are associated with periods of increased nervous tension. These people usually have marital difficulties and show other evidences of an inability to adapt themselves. You find them frequently in executive positions, but they are not good executives. A good executive knows how to delegate responsibility to other people, and when he has chosen a subordinate, he relies upon his judgment. When I was somewhat younger I did a great deal of examining for one of the large life insurance companies and I was assigned particularly to executives. The man who was the head of a large company was easily accessible, and when an appointment was made he kept it, and for the time assigned his desk was cleared and his telephone was silent. He was relaxed. The other type was usually found in a lesser position and was difficult to pin down as to time. When you did see him his office was a mad house with telephones ringing and people running in and out. As a result he was in a "lather." Invariably the story of some gastro-intestinal complaint would come to light. This man was insecure, he did not trust his judgment in picking subordinates, he was trying to impress his associates with how busy and intelligent he was, and usually his

business or department did not run efficiently. In and about all large cities you find various sorts of health organizations which cater to this type of individual. These vary from the masseuse and trainer found in his club, through the high class gymnasiums to the health farms and spas. These men eat and drink irregularly and unreasonably. The usual routine is black coffee for breakfast, crackers and milk for lunch and an enormous, heavy meal for supper preceded and followed by a variety of potent alcoholic beverages. Their vacations are repetitions of their way of life, unless they get to the point that they can no longer carry on and have what they call a "nervous break-down." Then any measure which will entirely remove them from their environment and place them in a well-ordered routine of exercise, rest and food intake, will effect a cure, providing the method of treatment sufficiently impresses them. This is where the health farm and spa enter the picture.

Now we come to a group that is far more difficult to analyze, and which is probably a great deal larger, but which perhaps does not impress itself on the medical mind so readily. During a civilized human being's transition from uterine life to the complicated adaptations of human existence the gastro-intestinal tract plays one of the most important roles. In infancy the whole existence of the individual centers around the intake of food and the excretion of waste products. Infants are terribly aware of their immediate surroundings, in fact much more so than at any later time in their life. They soon come to know that they can give pleasure to their parents by eating their food, or by defecating at the right time in the right place. Conversely they realize that they can punish adults or show their displeasure by withholding their stools or refusing to eat. All the primitive emotions of love, hate and jealousy are intimately linked to the fundamental bodily operations.

In addition, sexual and erotic sensations are intimately associated. That the lips receive a pleasurable sensation from sucking the nipple is perfectly true. When the child is weaned he sucks his thumb. This habit is broken and the sensation is transferred to his anal orifice. The sense of security is wrapped up in hunger and the satisfaction of hunger, and in later life the fear of starvation is the nucleus of insecurity. The act of feeding is also deeply associated with the feeling of being loved, and for an infant to be fed is tantamount to being loved. The emotion of possessiveness and all its implications such as jealousy, greed, and envy, become linked with hunger and eating. The thwarting of this emotion of possessiveness and of the wish to receive, leads to aggressive tendencies, that



is to take by force from others that which the child wants for himself. These feelings all center around oral incorporation and may be the origin of the first guilt feelings that the child experiences. Whenever these emotions become repressed, they inaugurate a permanent tension and through the autonomic pathways exert a chronic disturbing influence on the alimentary tract.

Anorexia nervosa is a periodic or chronic loss of appetite which may lead to loss of weight and ultimately to emaciation. It is to be differentiated from Simmond's disease where loss of appetite is secondary to a pituitary dyscrasia. This symptom complex is frequently seen in connection with different forms of psychoneuroses and psychoses; particularly in reactive depressions. Women after adolescence show this symptom more often than men. There is usually an associated amenorrhea and the uterus may be infantile or atrophic. It is interesting to note in certain instances that the infant will refuse the nipple, and this being too early to represent a resistance of the individual to his environment, must represent an inherent lack of flexibility in transition and adaptation. Superficial examination in cases of anorexia nervosa reveals many neurotic tendencies. Obsessive, depressive schizoid features and certain compulsive character trends predominate. Even the physician untrained in psychologic study can readily see that psychologic factors are of primary etiologic importance, but it takes a psychoanalytic survey to plumb the depths. Unconscious aggressive possessive impulses of envy and jealousy are the most important causative factors, and these impulses if depressed by the conscious can lead to inhibition of eating. Eating is a gratification, and a guilty conscience, even though it be unconscious, may not permit the patient the gratification of satisfying his hunger. It is a well-known fact that fasting is a form of repentance that eases a troubled conscience. Another, probably more important explanation is that not eating is an unconscious spite reaction. The adult reacts like a child and tries to hurt his associates and force them to pay more attention to him. This is a very common neurotic trait, that is the assumption of a symptom in order to draw attention to one's self and make himself the center of attraction, which could not be otherwise achieved. Such a condition is frequently encountered in wives of successful and popular men, who fully realize that they cannot compete intellectually for his attention, and who resort to the childish urge of making a nuisance of themselves. Eating is connected also with pregnancy fantasies, the idea having been fostered in many children and adolescents that pregnancy takes place through

the mouth. This idea may have been fostered by some older person who had subconscious perverted ideas. The unthinking rejection of pregnancy desires is a fantasy frequently found contributing to eating difficulties in young girls. In certain instances by no means infrequent, certain young girls find great difficulty in eating in the presence of men, particularly those to whom they are attracted sexually. This difficulty may spread to include people in general, and these unfortunate people get to the point that they can only eat alone or in the presence of their mothers.

We must now consider the opposite to these eating difficulties. Instead of anorexia, the appetite may be increased. This of course may be the symptom of organic disease such as diabetes mellitus or hyperthyroidism. In bulimia of psychogenic origin the increased intake of food does not represent a substitute gratification for a frustrated emotional tendency and may represent an increased craving for love or aggressive tendencies to grab or possess.

Nervous vomiting is an expression of a guilt feeling. Eating has an aggressive symbolic significance and the vomiting is the expression of a guilty conscience which will not allow the individual to retain that which he has obtained by aggression. This, like all neurotic symptoms of the gastro-intestinal tract, is only a manifestation of a general psychoneurotic disturbance.

In general, esophageal neuroses take two forms; one cardiospasm, and the other in which there is the sensation of a foreign body and the patient cannot get the food down. I suppose every doctor has encountered the patient who says that she cannot swallow pills and has to have her medicine in liquid form. The emotional basis for these symptoms is an unconscious rejection of incorporation, which is the result of aggressive impulses, often of a sexual nature, connected with eating and swallowing. Kronfeld compared the esophageal neurotic with the gambler. Both dare to put things in the mouth and expose themselves to an imagined danger. Disgust plays an important role, which is a combination of temptation and rejection. Cardiospasm consists of a contraction of the lower end of the esophagus which leads to a dilatation of the proximal portion. Superficially it belongs to the group of conversion hysterias, and appears when the patient finds himself in an emotional impasse in regards to his external situation. That there is a somatic factor is probable for it has been found in certain cases that have been examined histologically, that there is a loss of parasympathetic endings in the cardiac sphincter. The condition may be transient, recurrent or chronic. I remember one particular patient who was a sailor and his first attack occurred



while en route by plane to South America. He was destined for duty which though not dangerous, was extremely disagreeable in his estimation. The spasm was almost complete and lasted for several months during which time he was hospitalized. Finally he was promised a discharge from the service, and before leaving he was dilated several times and was completely relieved.

Stomach neuroses display a tremendous variety of manifestations based on motor and secretory disturbances and are extremely difficult to differentiate from organic disease. Frequently unhealthy eating habits will produce a gastritis which combined with functional disturbances of central origin make for a still more difficult differential diagnosis. The manifestations may vary from a slight distress after eating, heart burn, anorexia, regurgitation, eructation of gas, to severe gastralgia and intractable vomiting. These symptoms may be based on hypoperistalsis, hypermotility, hypersecretion, and hypersecretion of acid and pyloric stenosis. This condition may be the expression of hostile aggressive feelings when the patient is inhibited. Hypoacidity seems to occur most often in connection with depressive states and with fatigue of a chronic nature. In all patients suffering from psychogenic gastric disturbances, the repressed, receptive, help-seeking dependent tendencies play a predominant role. A strong fixation to the early dependent situation of infancy is always present. This is in conflict with the adult ego, hurts its pride, its wish for independence and self-assertion and thus becomes repressed. The individual is not well adapted to his environment and would unconsciously like to return to his dependent childhood but he overcompensates. These functional gastric disturbances are influenced by worries, fear, family quarrels, and business reverses.

It may be well at this point to consider the significance of emotional factors in connection with the etiology of peptic ulcers. This is a concept that is being emphasized more and more of late. Isolated observations over a long period of time has indicated that there is a definite and important connection. It is thought by Alexander that the changes noted in the gastric mucosa in connection with hypertrophic gastritis were the result of a functional disturbance characterized by hyperacidity over a long period. It is a fact that peptic ulcers will develop in a stomach that is the seat of a diffuse hypertrophic gastritis. That certain types of persons seem to develop ulcers more readily than others has been repeatedly observed, as has been the fact that certain races do not. Ulcer is a disease of the civilized world and affects chiefly the striving and ambitious men of the western civiliza-

tions. Draper and Touraine tried to describe the ulcer type psychologically as characterized by the presence of a masculine protest and rejection of female tendencies and anatomically as the asthenic or longitudinal type. Alexander does not believe that ulcers develop more in one type of personality than others, but instead there must be a typical conflict situation which may develop in many very different personalities. The typical conflict is between the desire to remain in a dependent infantile state as contrasted with the pride and aspiration of the adult ego for independence, accomplishment and self-sufficiency. Many an ulcer patient shows an exaggerated aggressiveness and does not want any sort of help, whereas deep in his unconscious he has a desire for the sheltered life of childhood. This explains why, after the ulcer develops, he is so often cured by being removed from his environment and put under nursing care. When the disease has progressed to the point where it is severe, he can openly give in to his repressed longings and give up the struggle for existence.

The person who wishes to return to the infantile life where being fed is associated with the feeling of security and love, has to repress this desire. The repressed longing to be loved and dependent mobilizes the innervation of the stomach which serves as a chronic stimulus and leads to its dysfunction. The stomach behaves at all times as though it were taking or about to take food. Under this chronic stimulation the stomach behaves constantly as it does during digestion, and chronic hypermotility and hypersecretion are the consequences. The empty stomach then is under the same physiologic conditions as the full one. Whether a constitutional or acquired weakness of the stomach is present to account for the fact that certain individuals get ulcers and others do not is a question which must be left unanswered at this time. Pylorospasm over a long period which does not allow for the usual reflux neutralizing of the stomach contents may be a factor. Also the blood supply may be affected.

The psychology of the excretory functions is in many ways similar to that of eating. Excrement plays a terrifically important role in infant life. One important factor is that it is something that is not talked about, and has been excluded to a great degree from social and medical talk. However, in the child the excretory function is something that is made a great deal of by the parent or nurse, and as a result becomes associated with possessiveness, pride and the tendency to give. A stool is a prize which the parent seeks and if the child is able to give it at the proper time and place, it constitutes a gift and an indication that the

child wishes to please. Also because the child learns early that the stool is something that is secret, not talked about and is considered dirty, he can develop certain hostile impulses connected with this function; that is, to attack, to soil, to disparage. He sees readily the disgust with which the adult handles a dirty diaper and at times must be confused when he thinks how much the adult wanted him to produce that stool a short time earlier. In addition, the child soon learns that there is a pleasurable sensation to be derived from retaining the stool in his rectum. This is an erotic area which takes the place of the lips and mouth when he is weaned from the nipple and broken of thumb sucking. In addition he finds that the adult has difficulty in interfering with that pleasure and the child develops a sense of independence in connection with it. He is urged by the adult to part with the excrement when it is convenient to the adult, and is frequently rewarded for the act, and so it becomes associated with the act of giving, especially giving pleasure to adults. Soon the excrement becomes associated with something dirty and evil, and the feeling of pleasure associated with it changes to disgust and deprecation. This is evidenced by many of the deprecatory acts, gestures and words that are directed towards the anus and feces by particularly adolescent or younger individuals. So we see that subconsciously the act of defecation can be associated with the giving of pleasure to others or with a hostile feeling towards others.

It is a great question whether the different forms of functional disturbances of the colon are manifestations or gradations of the same thing. That spastic colitis and chronic diarrhea ultimately develop into mucus colitis is probably true in many instances. There is little doubt that emotional disturbances play a large role in their etiology. How much these disturbances aggravate an underlying local organic disturbance, or whether they themselves constitute the whole basis, is a much mooted question. Simple diarrhea frequently is the somatic manifestation of a central disturbance based on a psychoneurosis. Frequently watery or solid stools, up to 20 and 30 a day, may well be connected with undue worry, and in such cases there are no organic findings. This sort of a disturbance causes a great deal of worry on the patient's part, and he dreads each successive defecation. In such a case the passage of the stool is not associated with pain or tenesmus. Simple forms of psychotherapy often alleviate the condition and at times cure it completely. I have in mind a patient who had such a diarrhea for a period of two years, which had not been helped by any sort of treatment while he was at

home. The mere changing of his locale affected a complete cure. He was sent home, but as yet I have not heard whether it has recurred. These patients are almost desperate in their desire to associate their symptoms with some organic disease. In some cases I have felt that they would be intensely relieved if they were told that they had a malignancy. It is needless to say that this would be a most drastic form of psychotherapy.

Mucus colitis is in all probability the manifestation of an autonomic imbalance with the parasympathetics in the ascendancy. But this in turn is probably due to an emotional instability of the anxiety neurosis type. These people are usually overconscientious, dependent, sensitive, anxious and have guilt feelings. They are suffering from conflicts, and perhaps the diarrhea is their outward manifestation of their desire to accomplish something concrete. Emotional conflicts and nervous tension are frequently found as the precipitating factors at the onset of the disease and also when recurrences appear. These people perhaps wish to compensate for wishes of dependency, by activity, and substitute an attack of diarrhea for real accomplishment. It is certainly characteristic of many of these people that they have all kinds of desires and talk a great deal about all the things that they plan to do and never really accomplish any of them. Their particular excuse is that they have not got the time. The diarrheal patient overcompensates for inactivity by an unconscious symbolism of the act of giving excrement. This produces a chronic stimulation of the peristaltic activity of the bowel through the parasympathetics. Perhaps certain women who for one reason or another do not wish or fear to have children, compensate for the lack of this greatest of creative functions by substituting an overactive bowel.

Although constipation may be due to organic causes, it is usually psychogenic. Superficially it may seem that the patient does not give enough time to the act of defecation. He does not go to the toilet regularly and when he does he does not allow enough time for the consummation of the act. He dwells too much on the printed word in regard to this bodily function and becomes unduly introspective. Perhaps more deeply it is a combination of the distrust of paranoia and the defeatism and pessimism of melancholia. He withholds the stools because he feels that people about him do not care and that giving is not worth while.

The asthenic or constitutionally inferior people present a somewhat different problem. In this group there is not necessarily the deep underlying psychologic disturbances that we have just discussed. They are tired, weak and lack energy and their symptom

complexes are usually due to an autonomic dysfunction. Their symptoms are not too pronounced and consist of mild degree of pyrosis, nausea and aerophagia, bloated and full feelings, belching flatus, constipation, fatigability, malnutrition and a certain degree of emotional instability. They are the type that show a hypotonic stomach that empties poorly. It may be said that in general the gradient of intestinal activity is very low and that it takes little or nothing to disturb it. Reverse wavelets are easily initiated. Digestive processes are slow, and alleviation of their symptoms presents a very difficult problem because there is so little to work on.

I have gone at some length into the psychologic disturbances which are thought by many of our best observers in the field of psychiatry to lie behind the various functional disorders of the gastro-intestinal tract, not because I think that an internist can be a competent psychoanalyst. It would be a great mistake for us to delve too deeply into these deep-rooted emotional conflicts. In many instances, after having gained the confidence of the patient, I see that they are on the verge of bringing to the surface a mass of suppressed emotions which I know I will be unable to cope with. When this occurs I am genuinely frightened and I know that it is time to call in a competent psychiatrist. The patient usually realizes this as well, so there is no great problem in this respect. However, the internist should realize that these conflicts do exist. He should be thoroughly aware that very definite pathways and patterns are present that make the somatic manifestations take the form they do. The person with psychogenic diarrhea did not pick out this particular symptom hit or miss. The internist should realize, as I have stated previously, that the patient is suffering, and that his symptoms

deserve just as much attention whether they be organic or psychic in origin. He should realize that well-worn, deep-rooted, subconscious pathways and patterns exist that have made these symptoms the outward manifestation of a neurosis.

It is also obvious that there are not nearly enough trained psychiatrists to handle all of these people. Luckily the vast majority of the patients with functional disease that consult us in our offices have a very mild form of the disorder. After we have thoroughly convinced ourselves that there is not organic disease as a basis, we can give these people a great deal of help if we try. Our prime objective is to give them some insight, which will make it much easier for them to get along with their symptoms. If we take sufficient time and exert enough patience, we can clearly explain that their symptoms emanate from a functional derangement of their intestinal tract, rather than from a disease process. We can further tell them that this derangement is incited by a conflict of emotions which affects the autonomic nervous system. It will not be advisable to go a great deal deeper. In addition one can give them advice concerning certain environmental disturbances which are obviously upsetting them, and suggest a philosophy that they might adopt. Then one can prescribe one or more of the various antispasmodic-sedative combinations that are on the market. The various secondary physical defects (malnutrition is the most frequent) which might be present can be corrected. By the time one has done all this one will have the patient's complete confidence and this is the most important part of therapy.

So in closing, let me say: be patient, be kind, be understanding.

1834 Connecticut Ave., N.W.

### Further Comments on Medical Journals in 1848

In the course of half a century from the establishment of the first of the Medical Journals, their number has been gradually rising, until at the present time, at least twenty are known to be in existence. Some principle in addition to the wants of the reading community, must exist to account for such inordinate fecundity in this particular department. This is to be found in the homely fact, that a medical journal is a convenient ally and advertising medium for public institutions and publishing establishments, and that by the *help yourself* system so generally established, it is not necessarily much harder to edit a medical jour-

nal than to furnish the "notes and additions" to the work of a British author. Still, the general character of these journals is respectable, and of several among them highly creditable to the state of medical science. Every year shows that exact observation is more and more valued, and that a better literary standard is becoming gradually established.

—From the report of the committee on medical literature. *Transactions of the American Medical Association*, Vol. 1, 1848, p. 283.

# The Challenge of Alcoholism\*

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Alcoholism presents a modern-day challenge to society and the medical profession. The proper prevention and treatment of excessive drinking implies a knowledge of the etiologic factors. In some cases these are obvious and remedial steps may be taken to correct them. In others detailed studies fail to bring out the dynamic energy behind the drinking. Of late the slogan, "alcoholics are sick people," has been placed before the public eye as a result of the National Committee for Alcohol Hygiene and the monograph bearing the same title written by Seliger.<sup>5</sup> It is certainly true that many alcoholics are immature, dependent, impulsive personalities whose ego weakness may be dissolved in ethyl alcohol in various forms. Many have not had the proper environmental associations and influences which are necessary to build a strong rugged personality during the childhood period. The analytic evidence points toward the fixation of the alcoholic in the oral incorporative or sucking stage. This may be due to acute frustrations following too early withdrawal of the bottle or breast or feeding delays. This interpretation of the character structure of the alcoholic may or may not be correct. Some feel alcoholism is evidence of latent or overt homosexuality with profound maternal attachment, lack of ambition and typical dependency. At any rate, these interesting and sometimes theoretical formulations are of little avail in treatment unless one has the time and financial background to undergo a complete personal analysis. Usually the alcoholic's finances are in such an anemic state, he is unable to assume any marked degree of financial responsibility.

The alcoholic drinks to narcotize his anxiety and predisposed ego, and some type of therapy within his means must be instituted.

The magnitude of the problem of alcoholism is evident and increasing daily. Haggard and Jellnick in "Alcohol Explored" have estimated the number of intemperate drinkers excluding the chronic alcoholics at 1,400,000 to 1,800,000. Adding to these, 600,000 chronic alcoholics, the number of intemperate users

of alcohol becomes 2,000,000 to 2,400,000. At least 50,000,000 use alcohol in the United States.

The vast majority of criminals admitted to the Colorado Psychopathic Hospital during the past years have committed their antisocial acts in a setting saturated with alcohol.

There exists in the mind of the average layman a tendency to equate alcoholism, insanity and crime. The old saying, "Was he drunk or was he crazy?" is frequently heard as a lay group discusses a recent gruesome newspaper headline. This thought-association has been readily pounced upon by the legal profession and the defense plea of "not guilty by reason of temporary insanity at the time of the commission of the alleged offense" is being utilized more and more in the courts of law. By clever cross-examination and shrewd questioning, a defense attorney can readily establish a suspicion of temporary insanity in the minds of the jury with a defendant who was drunk at the time of the crime. Rymer<sup>4</sup> has written an excellent article on "The Insanity Plea in Murder." Society as a whole will not permit the wanton slaughter of its members by intoxicated individuals and allow the perpetrator of the crime a few months' stay in the state mental hospital before being turned loose again to indulge in his "temporary insanity."

The problem of the alcoholic is concerned with personality deviations and character defects. This establishes it as a medical problem that falls within the realm of psychobiologic psychiatry. The intelligent alcoholic is often very clever in keeping the dynamics of his drinking to himself. There are as many types of alcoholics as there are personality patterns. The alcoholic has discovered an easy and what he feels is a temporary solution to all his personal difficulties.

The majority of alcoholics fall into that clinical "wastebasket" of psychiatric diagnosis and nosology called the psychopathic personality. Certainly all alcoholics are not psychopaths, but many psychopaths are alcoholics. Realizing full well that a study of human personality cannot be made with yardsticks or slide rules, the following general personality of the psychopath is presented:

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1. Normal intelligence.
  - a. As measured by psychometric and clinical appraisal.
  - b. A lack of adequate intellectual depth to personally understand his own behavior.
  - c. The cognitive subdivision of his personality seems to be ruled by primitive basic instinctual and sexual drives to the exclusion of rational behavior.
2. Psychopathy usually in the family history—one or both parents may evidence psychopathy.
3. Instability, unreliability with a failure to focus on any goal.
  - a. A lack of consistent consecutive employment with an inability to produce sustained effort coupled with—
  - b. Characteristic resentment of authority.
4. A constant tendency to project personal insecurity on the outside world in a typical manner by blaming others.
5. A lack of basic innate emotional control with multiple episodes of emotional impulsivity and lability. A lack of evenness of emotional tone with sudden, instantaneous, and uncontrollable emotional release coupled with motor activity of a rage reaction type resulting in—
6. Antisocial behavior with arrests and subsequent sociologic and punitive measures.
7. Egotistical, childish, narcissistic, wilful demand for immediate gratification with no regard as to the feelings and regards for others.
8. Frequent recourse to drugs and alcohol—certainly all narcotic addicts and alcoholics are not psychopaths yet the excessive use of these agents is commonly seen in many cases.

Some alcoholics are psychotic, and, when the alcoholic saturation has lifted, the psychotic pattern is revealed. Certainly some borderline psychotics are unable to maintain a marginal adjustment after indulging excessively in alcohol. The alcohol appears to act as a trigger mechanism in the psychotic explosion. Cases of this type were not infrequently encountered in the military service.

The term reactive alcoholism denotes drinking as a result of difficulties encountered in the external milieu such as marital, economic or sociologic difficulties.

Certain neurotics use alcohol for relief of tension and anxiety, and it may be a conspicuous symptom of the neurotic illness. The ego in the neurotic strives for a successful defense that will ward off disturbing feelings and frequently alcohol is resorted to in an attempt to allow discharge of the opposing impulses.

Certainly a characteristic of the chronic alcoholic is that he is at times unable to refrain from drinking, yet this drinking is frequently a symptom expression of an underlying neurotic, psychopathic or psychotic personality. Assuming that he is not psychotic, then his alcoholism must be viewed as a symptom, just as tremor of the hands, hyperhidrosis, palpitation, or constipation are looked upon as neurotic symptoms.

Juries do not feel the above symptoms constitute temporary insanity, and no one has heard of a verdict of not guilty by reason of enuresis or somnambulism. Yet the drinking is a volitional expression of tension and is, to some extent at least, volitionally controlled. No one pours the alcohol in the hair of the accused or forces it down via stomach tube—he, of his own will, consumes it. Certainly, some alcoholics may even experience a true "black out" or so-called alcoholic amnesia. In a real amnesia one finds fragmentary or cloudy memories. All too frequently the claimed encapsulated amnesia is the result of a self-preservative instinct when the accused is threatened with the gas chamber or life imprisonment.

The thoroughly intoxicated person certainly is at times unable to distinguish right from wrong, but he certainly possessed the capacity to adhere to the right before he started his alcoholic debauch. Society and the medical profession cannot tolerate the "temporary insanity as result of drinking" or the liquor bottle will serve as a permit to commit homicide.

The cost of alcoholism to society is tremendous, and conservative estimates run at about a billion dollars a year including maintenance of drunken persons in local jails, hospital and medical care, crime, accidents and potential wage loss.

The following analysis of the economic aspect of alcoholism has been prepared by Landis.<sup>2</sup>

#### *Expenditures Probably Referable to Inebriety—1940*

	THOUSANDS OF DOLLARS
Mental—hospital care and treatment	12,845
Bodily diseases—care and treatment	18,480
Accidents—injury, property damage, etc.	89,170
Maintenance of drunken persons in jails	25,550
Crime—various items	188,560
Support of dependent persons (private)	21,220
<b>Total</b>	<b>355,915</b>
Less 2.5 per cent correction for probable duplications	8,898
<b>Net total</b>	<b>347,017</b>

#### *Potential Wage Loss in 1940—Certain groups*

Persons mentally ill	17,060
Bodily illness of wage earners	24,000
Mobile inebriates in jails	78,120
Persons involved in accidents	118,800
Prisoners, Federal and state	35,348
Absentees in industry	169,632
<b>Total</b>	<b>442,960</b>
Less 2.5 per cent correction for probable duplications	11,074
<b>Net total</b>	<b>431,886</b>
<b>Grand total</b>	<b>778,903</b>

It is obviously not an estimate of the social costs of all drinking; expenditure for treatment of the inebriate habit is conspicuously absent.

It is felt that without a doubt drinking is on the increase in the United States. We are readjusting and attempting to relax following history's most tragic war and frequently the desire to relax and let off steam leads to the local tavern or an endless round of cocktail parties. History has shown that heavy drinking often has followed great wars. When anxiety is deep and widespread, people often drink more heavily.

On March 2, 1944 the Department of Commerce<sup>1</sup> published estimates of the total value of alcoholic beverages purchased by the people of the United States from 1934 to 1943. The total amount estimated as spent in 1934 was \$2,003,000,000; 1940 was \$3,595,000,000; and for 1943, \$6,083,000,000. It has been estimated that around seven billion dollars was spent in 1946 for alcoholic beverages. Four billion dollars was spent last year for medical care by the people of the United States. It is apparent, then, that financially we attach more importance to the warm glow of alcohol than to our own public health. During the same period the national income increased rapidly and the rate of taxation generally increased. The reported expenditures for alcoholic beverages have apparently been equal to between 4 and 5 per cent of the total income of all the people during the years 1934-43. For the 131,669,275 persons resident in the United States, the expenditure of \$3,595,000,000 in 1940 was the equivalent of about \$27 plus per capita. For the approximately 44,000,000 users of alcoholic beverages, it was an average of about \$81 per person per year.

Many veterans faced with problems of readjustment, re-employment, housing, and the abrupt change to civilian life have sought solace at the bar where they can relive their war-time experiences and attempt to find someone who speaks their own language.

Funds available for the treatment and research of alcoholics are pitifully small when compared to tuberculosis, infantile paralysis, and cancer; yet who can measure the cost in mental deterioration, broken homes and the distortion of potentially useful citizens?

A statistical review of first admissions for alcoholic psychoses and alcoholism at the Colorado Psychopathic Hospital from January 1931 through December 1945 as shown in Table 1.

A rough scattergram of the age incidence of alcoholics in this series of admissions revealed the heaviest scatter to be in the 35-43 year bracket. At this time in life, the average person has accepted responsibility and is looking carefully, at times apprehensively, into the future.

TABLE 1

*First Admissions for Alcoholic Psychoses and Alcoholism, Colorado Psychopathic Hospital*

YEAR	PERCENTAGE OF TOTAL ADMISSIONS
1931	5.2
1932	5.1
1933	6.7
1934	11.5
1935	13.4
1936	10.6
1937	10.1
1938	10.2
1939	11.5
1940	11.1
1941	8.5
1942	11.2
1943	11.2
1944	9.8
1945	9.3
1946	12.3

It is interesting to note the increase in 1934 which may be a reflection of the repeal of prohibition. At the present, about one out of every ten admitted to Colorado Psychopathic Hospital is an alcoholic.

In reviewing a statistical analysis for readmissions to the hospital, it was found that out of all causes for readmission without psychosis, alcoholism was the leader; e.g., in 1943 alcoholism accounted for 59 per cent of all readmissions without psychosis. The present hospital policy regarding the admission of alcoholics is by necessity a rather firm one. The community has outgrown the facilities of the hospital, and, if all alcoholics were accepted, an additional nine to ten stories of hospital space would be required.

Many physicians refuse to have anything to do with an alcoholic. A cross-section survey of New Jersey physicians was made for the New Jersey Commission on Alcoholism and Promotion of Temperance by Riley and Marden.<sup>3</sup> They found that the average physician feels the chronic alcoholic is a sick man both physically and mentally and that the medical profession occupies a strategic role in any program dealing with the alcohol problem. This survey further showed that each physician saw on the average about seven alcoholic patients per year and that about half referred the patients elsewhere. The physicians who treated alcoholics used sedative and vitamin therapy, and very few took any steps toward long-term rehabilitation.

One of the recent psychiatric advances to spring from World War II was that of group therapy. Soldiers were found to feel, think, and act in a way that characterized them as a group which was quite different from that which characterized them singly. They developed an esprit de corps or experienced a feeling

of belonging to a certain unit or organization. The psychiatric casualties of a given unit, either in combat or a noncombat situation, were inversely proportional to organizational morale. If the morale were high, the psychiatric losses were low and vice versa. Among alcoholics, there is a common problem; hence, a group feeling is easily and readily established.

The average individual alcoholic usually resorts to alcoholism as a "flight into drinking" because of difficulty in adaptation to a group. The attitude of the group, whatever it may be—the family circle or business associates—at times forces the feeble ego to express itself in drinking; hence, the common existence of rejection and feelings of inferiority experienced by the alcoholic. He lacks a sense of belonging and group participation. At times his drinking may be an expression of aggression directed toward the group for any rebuke or condemnation he felt he might have received. The group then regards his drinking as an asocial, amoral, disgraceful type of behavior, and the resultant exaggeration of inferiority when he is sober, establishes a vicious circle.

When the alcoholic has sufficiently detoxified to be approached on a therapeutic basis, the first initial stumbling block encountered by the therapist is a marked hostility directed toward the therapist and the hospital itself. Alcoholics bitterly reject their incarceration in a mental hospital. The uninitiated still regard psychiatry and psychiatrists with skepticism. Many still feel there is a certain stigma attached to being hospitalized in a mental hospital. The recent appearance of a series of pseudo-psychiatric movies has fostered a mass media of popular misinformation regarding the psychiatrist. Resistance to psychotherapy is sometimes based on inadequate knowledge and misinformation. Much time and money spent on treatment could be saved were it not so often necessary, first, to dispel a patient's misapprehensions about psychiatry. The fear and apprehension of delirium tremens and the sobering-up period are severe enough without the presence of disturbed psychotic patients.

The therapist usually represents to the alcoholic an authoritarian figure from society and from whom he can expect more criticism and social rebuke for his drinking.

It is felt that absolutely nothing can be gained by utilizing a punitive or threatening attitude toward alcoholics. They are as well aware of the fact they may die some day of cirrhosis of the liver as is the physician. It is felt that direct lecturing will be to little if any avail. The alcoholic should not be told that he is lacking in will power or that he is a weak-

ling. He need not be reminded of the manifold inconveniences he has caused his family or society.

In conducting group therapy the physician should be well aware of the personality assets and liabilities of each member of the group. He should have a working knowledge of the dynamics of each patient's drinking problem firmly in hand. The first two sessions are usually devoted to a discussion of the physiology of alcohol. The therapist gives a brief talk the first 15 or 20 minutes of the session, and then discussion comes from the group. This affords an opportunity to eliminate from the group any intractable neurotics, psychopaths or borderline psychotics who might impede the progress of the group as a whole. One or two improperly chosen patients can ruin an entire group. During the next session one of the patients writes on a blackboard any and all suggestions from the group on the topic of "Why people drink to excess" and "What is an alcoholic?" It is amazing to learn how many patients, although they have lost their job, home, friends, and have been repeatedly institutionalized, refuse to admit to themselves that drinking is a problem. At this point each member is given a questionnaire similar to that designed by Grapevine, the official organ of the Alcoholics Anonymous. This affords the patient an opportunity to develop the history of his drinking in a chronologic order and to correlate it with life events. The answer to each question is made by merely stating the age at which certain events occurred; e.g., experiencing a blackout, starting sneaking drinks, starting using eye-openers, etc. Inasmuch, as the questionnaire is simple and direct, full co-operation is usually attained. A discussion of the topics in the questionnaire by group members usually occupies several sessions. By this time, the patients have lost their isolation and feeling of loneliness and realize their problems are not unique. Some friendships do develop, although usually they are on a superficial level. Interest is apparent over the other fellow's problem and his reaction and behavior during his attempts to "stay on the wagon." It is not unusual for the group to challenge the therapist with the attitude, "What do you know about it—you've never had D.T.'s." The group therapist, therefore, has the function of maintaining a group emotion between patients and between patients and himself. It is best not to accept the challenge but make a swift transition from the effects of drinking to the motivations of drinking, which is easily done.

In the main, after the first few initial sessions, the therapist becomes a patient listener and guides the discussion along desired lines. At times he initiates discussion at the beginning of the sessions and quickly



detects any group formations that may be utilized to achieve therapeutic ends. Infancy and childhood, adolescence, hostility, aggressions, inferiority feelings, feelings of inadequacy, social inhibitions, mental mechanisms of repression, projection, etc., and sexual adjustment are all topics for discussion depending on the intellectual capacity and emotional insight of the particular group involved. The emotional nucleus from which the best therapeutic clinical results are obtained in the patient to patient and patient to physician identification and rapport. At the last session, one of the leaders of the A.A.'s gives a talk outlining the functions of that organization. This allows the patient to transfer the group feeling from the hospital to society and augments a more favorable prognosis. Weekly out-patient follow-ups with the physician are advised.

At the present, it is too early to evaluate the success of this type of group therapy. At least, it is a step forward to meet the challenge of alcoholism.

Group therapy is certainly not an adequate substitute for individual psychotherapy; however, it has an advantage in that it saves time for the physician and allows him to spread his therapy to a greater number of patients.

The group therapeutic approach is certainly not one of pure cold intellectualization, but, rather it offers a possibility of emotional and affective resynthesis and reintegration of the personality. It serves also as an opening wedge for individual personal psychotherapy. The patient not infrequently hears in the group life experiences of others that are closely akin to his own, and this allows some emotionally charged and repressed material to come out in the open and be discussed with the individual therapist. If the group therapist can bring the patients to admit to themselves the seriousness of their drinking problem and instill an incentive toward getting well, then the problem of individual therapy is lessened.

Alcoholics as a group are more amenable to group therapy than any other class of patients in the psychiatric hospital.

Group therapy according to Glueck<sup>6</sup> accomplishes the following: (1) Resistance to treatment is greatly lowered; (2) transference to the therapist is facilitated; (3) interpatient transference is easily established; (4) verbal material and acting out occur at a greater rate and with greater facility than can possibly take place in individual treatment; (5) groups offer some possibilities for treatment that individual therapy does not; and, (6) by and large the discussions by the patients deal with immediate and empirical problems.

Some comments regarding group therapy by various

members follow: "I think it's all right, you can't do too much about the proposition of alcohol. I think it's somewhat similar to the A.A.'s and they seem to be making headway" . . . and "Makes us all more aware of our personal problems" . . . or "There's one thing I like especially and that's to have several fellas talk over drinking in a serious manner." . . . Another member stated, "Instead of joking about it while in the hospital, it makes a fella get down and think a little." A physician alcoholic said, "I like to get the reaction from other parties who are more or less in the same situation I am."

It is seen then that members of the group verbalize their feelings about finding others with a similar problem. This augments the supportive value of group members to each other.

The Thematic Apperception Test and the Rorschach are important adjuncts in treating the alcoholic inasmuch as they are "projective" technics. It has been shown that "play technic" is of inestimable value in solving child behavior problems inasmuch as the little child projects his problems and works out aggressive tendencies onto the toys and dolls that he plays with. He dramatizes situations that reveal his basic feelings and conflicts.

The Thematic Apperception Test similarly may help reveal the dynamics in the personality of the alcoholic by allowing the patient to construct his own fantasies and productivities. His own conflicts may be projected into the stories developed by him.

A Rorschach Test is an ideal and time-saving technic which uncovers the basic personality structure. Intellectual capacity and efficiency, sexual difficulties, anxiety, affective and emotional control, aggressive submissive ratios, inner conflicts, ego strength, capacity for a rich mental life, obsessive-compulsive trends and other personality facets are demonstrated by the Rorschach. It can be administered as a yardstick in measuring progress during therapy.

Alcoholics appear to be especially amenable to the use of intravenous amytal for amytal interviews. This may possibly be due to the simulation of the euphoria produced by alcohol. Narcotherapy facilitates relaxation and makes it easier for the patient to speak. It usually brings the physician and patient into closer rapport. It has a strong appeal to the alcoholic because it utilizes a physical means of approach. The possibility of addiction if narcotherapy is prolonged should certainly be considered. A technic of this type facilitates the expression of repressed aggression and feelings of inferiority and inadequacy. The ultimate goal of the process is to fuse ideas with feelings and to mobilize affects so that an attempt is



made to reintegrate the emotional life of the patient.

The efficacy of public out-patient alcoholic diagnostic clinics as organized by the Yale Plan has been proved. A program of group and individual therapy for alcoholics at public clinics is a necessary part of a sound community and public health structure.

As in other personality disorders, the family background plays a significant part. A well-adjusted mature individual seldom relies on alcohol as an escape or a means of handling his problems; therefore, it may be said that all the conditions that go into making a child into a physically and mentally sound adult, will help in preventing his ever becoming an alcoholic. Alcoholism is a group problem and a group responsibility.

### CONCLUSION

The medical and sociologic problem of alcoholism is increasing daily. Most alcoholics are unable to undergo protracted care and treatment due to inadequate financial capacity. Society must protect its own members against homicide occurring as a result of alcoholic saturation and the legal defense of "temporary insanity." Drinking must be looked upon in some cases as a symptom expression of underlying tension and anxiety and should be considered as a psychoneurotic manifestation. Many drinkers possess an inadequate and loosely integrated personality classed as a psychopathic personality which demands immediate and instant gratification of its desires.

There is an urgent need for funds to be used for research into the problem of alcoholism. At the Colorado Psychopathic Hospital during 1946, 12.3 per cent of all first admissions were for alcoholism with or without psychosis, in spite of a rigid admis-

sion policy necessitated by available bed vacancies. Nothing can be gained in treating the alcoholic by the use of direct lecturing or punitive measures. Group therapy is an important adjunct in treating the alcoholic and the patient to patient identification frequently serves as an opening wedge for individual therapeutic methods. Psychologic projective technics such as the Rorschach and Thematic Apperception Test frequently aid in disclosing the dynamic energy behind the drinking.

The gains achieved in the hospital by means of medical and psychiatric treatment are all too often limited and temporary. For this reason, close liaison with the A.A.'s has been established which allows the patient to transfer the group feeling obtained in the hospital to society at large.

### BIBLIOGRAPHY

1. Bureau of Domestic and Foreign Commerce: Consumer expenditures for alcoholic beverages (Press release, March 2, 1944), Washington; U. S. Dept. of Commerce, 1944.
2. Landis, Benson Y.: Some economic aspects of alcohol problems, *Quart. J. Stud. on Alcohol*, 1:79 (June) 1945.
3. Riley, J. W., Jr., and Chas. F. Marden: The medical profession and the problems of alcoholism, *Quart. J. Stud. on Alcohol*, 7:240 (Sept.) 1945.
4. Rymer, Chas. A.: The insanity plea in murder, *Am. J. Psych.*, 98:690-697 (March) 1942.
5. Seliger, Robert V.: *Alcoholics are Sick People*, Oakridge Press, Psychological Book Service Division, 2030 Park Ave., Baltimore 17, Md.
6. Glueck, Bernard: *Current Therapies of Personality Disorders*, New York, Grune & Stratton, 1946.
7. Strecker, Edward A., and Franklin G. Ebaugh: *Practical Clinical Psychiatry*, 5th Edition, Philadelphia, Blakiston, 1940.

### Sex Ratio in Cancer

The notion that cancer is primarily a woman's disease is false, the American Cancer Society states. In 1946, it is estimated, cancer killed 87,777 males and 93,723 females in the United States. The difference is only 6 per cent.

The reason many people think of cancer as a woman's disease is probably because of the large amount of cancer in the female sex organs. Cancer of the uterus accounts for 19 per cent and cancer of the breast for 18 per cent of the cancer deaths in women. While cancer of the breast can occur in men, it is relatively rare.

When it comes to cancer of the stomach and digestive system male deaths outnumber female by about 7,000 each year. U. S. Bureau of Vital Statistics reports for 1944 show 42,351 deaths among men from cancer of the digestive system as compared to 35,637 among women. Finally, more men than women die of cancer of the skin, mouth and pharynx, lungs, nervous system, urinary tract and other sites.

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# Cases from the Medical Grand Rounds Massachusetts General Hospital

Edited by LEWIS K. DAHL, M.D.

BOSTON, MASSACHUSETTS

## CASE 15

### PERNICIOUS ANEMIA

DR. MYLES P. BAKER: We are presenting a case of anemia with some rather unusual features about it which I hope will give rise to discussion as regards the treatment and natural history of this patient's illness. Dr. Odland will present the case.

DR. GEORGE F. ODLAND: The patient is Miss K., No. 123064, a 22-year-old girl of Lithuanian extraction, who was admitted to this hospital for the third time on February 3, 1947. Her complaint at the time was extreme weakness. Her first admission was in 1938, at which time she had a classical picture of thyrotoxicosis with a BMR of plus 53. After the usual pre-operative treatment a subtotal thyroidectomy was done, and her BMR was minus 10 when she was discharged. She returned to the Thyroid Clinic and was followed, and although apparently doing well she developed some mild thyrotoxic symptoms over the course of a couple of years. In 1940 she was found to have a BMR in the neighborhood of plus 23. Then she disappeared, being treated by her local doctor, until January 1946, at which time she entered the Clinic with a BMR of plus 56; she came into the hospital for her second admission in January 1946.

Again she was treated pre-operatively in the Medical Service, this time having thiouracil and iodine, and after a rather slow response was given another subtotal thyroidectomy. This time she had a persistent postoperative hypocalcemia and a minimal minus metabolic rate. She has been followed in the Thyroid Clinic and she has been treated by her local doctor who is giving her calcium and iodine.

Her present illness began roughly in September or early fall of 1946, at which time she began to notice increasing weakness and fatigability. Before October some of her friends noticed that she was somewhat pale, and by October her weakness had forced her to stop working. Her weakness, dyspnea, dizziness, and faint feelings progressed right up to the time of admission. The most marked increase in symptoms was in the last month before admission. She had noted some minimal ankle edema.

She walked into the Emergency Ward on the night of February 3, looking extremely pale. At that time the past history was obtained and blood studies were done on the patient. Admission red count was a little under 500,000 red cells per cubic millimeter, with a white blood cell count in the neighborhood of 3,000. Hemoglobin, as nearly as could be established on a Sahli hemoglobinometer was about 2 Gm. Her spun hematocrit was 8 per cent, and yet the patient was able to stand at the side of the bed on physical examination and complained only of some dizziness.

Physical examination showed a tall, somewhat thin, but fairly well developed female, who appeared in no immediate distress but was extremely weak. She had no complaint lying in bed. Her skin was dry, extremely pale, and had a peculiar brownish-yellow tint to it; the sclerae were clear. The tongue was somewhat smooth, although she had not complained of a sore tongue in the past. Examination of the chest was negative, other than the finding of a rather enlarged heart with pronounced apical and basal systolic murmur and a suggestion of gallop rhythm which was not heard by all examiners. The abdomen was soft, with the liver down about three fingers but not tender. No spleen was felt. Neurologic examination revealed present knee jerks, absent ankle jerks, and vibration sense was judged to be normal.

Examining the blood smear, which was in this case diagnostic, one saw a large number of oval macrocytes, a considerable variation in the size and shape of the red cells, multiple nucleated red cells, a considerable number of polychromatophilic cells and a decrease in the number of platelets. No other laboratory studies were done at the time. A diagnosis of pernicious anemia was made by the house staff and confirmed in the morning by Dr. Richardson and Dr. Baker. On the night of admission the patient received 70 units of liver extract intramuscularly.

The hospital course can best be followed by examination of Figure 1 which is more or less self-explanatory of the response the patient had.

DR. BAKER: This girl looks a lot better after the week here in the hospital. The points that, I think, we should observe this morning are her general build,

## Blood Indices

## PATIENT

## NORMAL

Color Index	1.3	1
Mean Corpuscular Volume	160	80-94 micra <sup>3</sup>
Mean Corpuscular Hemo- globin	40	27-30 micro micrograms
Mean Corpuscular Hemo- globin Concentration	25	33-38 per cent

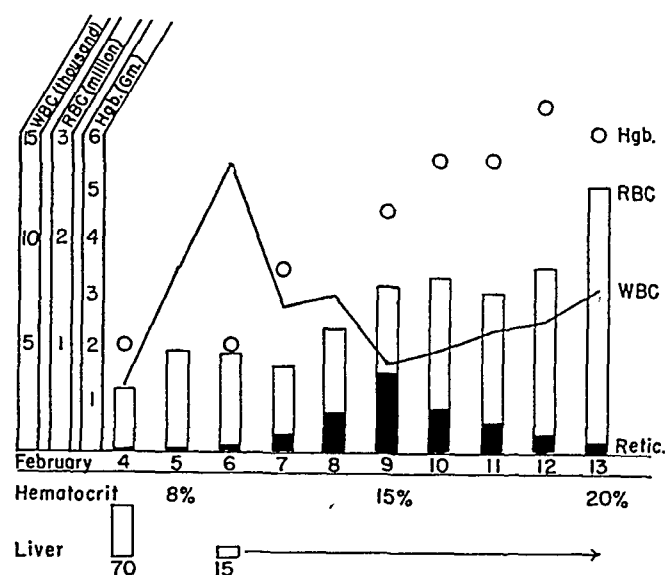


FIGURE 1

so different from what I have been taught to think of as the type of individual who develops an Addisonian pernicious anemia; the persistence of prominent eyes, the prominence of which we have not measured at this admission; the color of her eyes which are bluish; the general shape of her hand, the length of her fingers. There are no other physical signs to demonstrate this morning.

Are there any questions?

DR. WYMAN RICHARDSON: The tongue has been normal? It was normal in the beginning?

DR. BAKER: I think it had a rather smooth tip.

We are presenting this case as one of a macrocytic anemia with a high mean corpuscular volume, without proved achylia gastrica, because we have been unable to prevail upon the patient to let us put down a tube. We don't know just why this is and still have hopes that perhaps before she goes we will be able to do so. Nor have we a bone marrow biopsy, nor a chance to see what the effect of omitting treatment with an adequate amount of antipernicious-anemia principle would be; i.e., whether a relapse would follow, but we believe she has pernicious anemia on the basis of the blood picture which has been described, and on the basis of her highly indicative reticulocyte response to liver extract parenterally.

The question of the treatment of such an initial picture of pernicious anemia, I hope Dr. Richardson will discuss. Perhaps this girl has had more liver extract than she needed. If so, is there any advantage in the accumulation of antipernicious-anemia principle as the result of giving more liver extract than may be necessary to produce the sort of specific response and general subjective improvement that is so obvious in this girl?

The question of transfusion came up on the night of admission on this patient whose red count was below one million, and there was some talk in the morning following as to what would have been the likelihood of an unfavorable reaction to transfusion within a few days. I believe that circulatory collapse has developed following transfusion in pernicious anemia cases and I hope Dr. Richardson will comment on that.

The case interested me also because of this association of hyperthyroidism and the pernicious anemia which we believe this girl has. The association of the two diseases has been commented on by others, and I hope Dr. Means, who saw this patient on both the previous admissions and may remember her, will comment on this association. There is an interesting article published about ten years ago in the Hopkins "Bulletin" following a study of one case by Dr. Andrus and Dr. Wintrobe.\* A few other cases that had previously been in the Johns Hopkins Hospital were reviewed. It was their feeling that the association of the two diseases was entirely fortuitous. It was pointed out that three, and perhaps four, of their cases, all showing the two diseases, had hyperthyroidism develop after pernicious anemia. They developed characteristic hyperthyroidism either while under treatment for pernicious anemia in remission or, in one instance, I believe, in relapse. Last year in the Annals of Internal Medicine, a case similar to this girl's, save for the older age, was reported from a New York City Hospital.† This case had developed typical pernicious anemia about seven years after a previous subtotal thyroidectomy for hyperthyroidism, and then developed a recurrence of thyrotoxicosis during treatment for pernicious anemia. They commented on the fact that some 75 cases of this association of the two diseases had been reported in the literature, most of them scattered single cases, but in some instances, as many as six to eighteen such cases under the observation of one observer. They, too, came to the

\* Andrus, E. C., and M. M. Wintrobe: A note upon the association of hyperthyroidism and pernicious anemia, Bull. Johns Hopkins Hosp., 59:291, 1936.

† Bornheim, A., D. Schwimmer, and T. M. McGavack: The combination of hyperthyroidism and pernicious anemia, Ann. Int. Med., 23:869, 1945.

conclusion that it was entirely a fortuitous association, that there was no common etiologic factor. The thyrotoxicosis is definitely more than just the elevated BMR seen in some cases of pernicious anemia in relapse. About three-quarters of these individuals have a story of hyperthyroidism first and then subsequent pernicious anemia. As a rule they are in the younger age groups, and in females.

There is another interesting report from Cook County Hospital, published a year or so ago, of what the authors chose to call atypical pernicious anemia, occurring in young people.<sup>‡</sup> This girl is 22 and their nine cases were all in women, most of them between 25 and 30. The authors point out that in these young women the pernicious anemia took an unusual form, with fever, palpably enlarged spleen, and rather turbulent heart actions with murmurs that strongly suggested active rheumatic heart disease. In some instances the clinical picture at first brought to mind subacute bacterial endocarditis until the true nature of the anemia became clearer. This girl did have fever on admission, but as Dr. Odland has said, did not have an enlarged spleen, and the elevated rectal temperature has quickly become normal under treatment.

There is certainly no question about this girl's antecedent thyrotoxicosis. She continued to be a rather emotionally unpredictable person. We have had no other BMR this time. I think her last rate in December was minus 17 per cent.

Dr. Richardson, would you like to comment on the treatment in this case and on any other point you are interested in?

DR. RICHARDSON: I would love to. In the first place, what is your definition of pernicious anemia? I call pernicious anemia any anemia which is relieved by the use of the liver principle or, more specifically, by the use of fraction G or some derivative of it. This patient, therefore, has pernicious anemia. She has, I believe, a true pernicious anemia in that she will always have the tendency, although the length of the remission cannot be predicted. If you withhold liver to see whether she will get along without it, this is just the type of patient on whom you have to be sure that you have a positive follow-up. When such patients go into relapse they develop a very common symptom, namely, obstinacy, an obstinacy which manifests itself quite frequently by a great reluctance to consult physicians. So it is a dangerous thing to withhold liver. But I think you are justified when her blood comes up to normal to stop it if she can be carefully followed. She might conceivably have a very long remission,

without requiring liver. However, I feel quite sure that she will turn out to need regular doses of liver for the rest of her life.

The longest remission that I know of occurred in a patient who is still living. She was seen in 1914 by Dr. George Minot in this hospital, who made a flat-footed diagnosis of pernicious anemia. Whether she then had transfusion or not, or whether she simply received a special diet in which Dr. Minot then was interested, I don't know, but she did have a remission and remained well for 14 years until she was again seen in 1928 with true pernicious anemia. She received an experimental fraction and did well and has been doing well ever since.

In regard to the association with thyroid disease, we found several patients with thyrotoxicosis in the group we were studying. The ones I remember developed the thyrotoxicosis after the anemia. I think it is more common to see the association of pernicious anemia and myxedema. One of our very earliest patients was sent in for myxedema and we found he had pernicious anemia, and laughed up our sleeves at the doctor who sent this pernicious anemia patient in as myxedema. Just before we discharged him we found his basal metabolic rate was minus 45. It seems to me that patients with hypothyroidism or myxedema may have a true pernicious anemia which will respond to liver even though you leave the thyroid alone, but they may also develop an anemia which will not respond to liver and will respond to thyroid. And there may be a few who have to have both liver and thyroid.

The youngest patient I know of in the hospital group was a young man between 22 and 24. Whether the thyroid disease has precipitated an inherent tendency to pernicious anemia in this girl, I don't know. Dr. Lerman, I believe, pointed out that patients with thyroid disease who developed anemia were the ones who had pre-existing achlorhydria. Am I correct?

DR. JACOB LERMAN: Yes.

DR. RICHARDSON: It may have precipitated the disease, but I feel quite certain she has a pernicious anemia tendency. Why do I say it? I don't know quite why I do say it. She does not have large ears; but she does have a rather broad face, I should say, wide-apart eyes, which are blue, and she has a sort of mouse-colored hair which will probably become sandy gray before very long.

This patient represents the old-fashioned pernicious anemia which now you almost never see. The new pernicious anemia is entirely modified by the fact that most patients get liver very quickly whether or not they have pernicious anemia, and usually iron too, and quite often penicillin or what have you. And the result is that we do not see patients with the severe type

<sup>‡</sup> Schwartz, S. O., and H. Legere: Atypical pernicious anemia of young adults, *Am. Jour. Med. Sci.*, 206:1, 1943.

of pernicious anemia that we used to see. This blood picture is as near that of a blood crisis as I have seen in at least 20 years. The blood smear was really fantastic. It showed those great big nucleated red cells, megaloblasts, and she had the Cabot rings that were described by Dr. Richard Cabot, which we don't see any more, and all kinds of things. And it did not take a hematocrit and all the alphabet studies to know that this was macrocytic pernicious anemia.

One other interesting thing is that the leukocytosis began two days before a measurable increase in the reticulocytes occurred. If you want to know whether a patient is going to respond to liver, the leukocytosis is the earliest measurable evidence.

And that brings up the question of transfusion. This patient has nearly as low a red cell count as any in the original group we studied. I think our lowest was 440,000, but those counts are apt to be inaccurate. The question of transfusion, I think, should be decided on the basis of the patient's clinical condition. You pointed out that this girl was in remarkably good condition in spite of the red count of 500,000. So it seemed to me safe not to transfuse her. Furthermore she happened to have a very unusual type of blood. Dr. Minot felt originally, and I feel the same way, owing to experiences we had with one or two patients, that transfusion during the reticulocyte peak or during the marked response was dangerous. We thought it was dangerous because we had several patients who developed serious thrombosis, both venous and arterial. Whether that is a valid observation or not, I am not sure, but I have taken the stand that you should not transfuse these patients unless you feel that they are not going to survive for one week; as a matter of fact, transfusion is almost never necessary. When I have used it, I have used it in rather old people who were confused mentally or semicomatose.

Now you speak about the basal metabolic rate. Remember that the old-fashioned pernicious anemia patient always ran a fever. That was characteristic of the disease. Well, the new-fashioned ones rarely have a fever. The basal metabolic rate was usually increased in those cases with anemia and without central nervous system symptoms and usually decreased in those patients with central nervous system symptoms without, or with very little, anemia. And in patients with both central nervous symptoms and severe anemia, we didn't know what the basal metabolic rate was going to be. In those with severe combined system diseases, it seemed to us they had many symptoms suggesting hypothyroidism and they seemed to do better with the use of small amounts of thyroid.

I will just say one more thing, about the amount of

liver. Theoretically, she got 70 units of liver. What is a unit? It is a very rough measurement. It is supposed to be that amount of liver which, when given daily, will just produce a maximum response. But it is obviously a very uncertain measurement, so the principle of treatment is to give too much. You cannot do any harm by giving too much, except from an economic standpoint. Seventy units given during the first night should be sufficient to produce a maximum response both from the point of view of the reticulocyte curve and total clinical response. However, one would like to play it safe. I would have cut out the daily doses and would have given 30 units every week until the patient's red cell count was over 5,000,000 and then I would space it out with the hope of being able to give it every four weeks. I don't believe in giving liver at longer than four-week intervals. Although even that may be too much, I think these patients should be kept with a high liver extract reserve or they will get into trouble. Well, I have talked too much, I could go on all day.

DR. BAKER: Dr. Means, would you like to comment on this case?

DR. JAMES H. MEANS: I won't say very much, because Dr. Richardson has covered many of the points. But this case does interest me on account of the association with thyroid disease. I think these two diseases are probably unrelated. Dr. Richardson mentioned one patient that we had with myxedema and pernicious anemia. There were two, as a matter of fact, that had both diseases and who required both liver and thyroid to maintain a normal existence. Then there were quite a flock of others on whom Dr. Lerman and I published a report. They did not have real pernicious anemia, but ordinary secondary anemia and did better with iron and thyroid than on thyroid alone. Now, there have also been a few who have had pernicious anemia and thyrotoxicosis, coincidentally, but I do not believe that there is any causal relationship between these two diseases either. I think it is a chance association. You mentioned, Dr. Baker, that this girl had a minus 17 BMR in December. As I recall the note in the Thyroid Clinic from our study at that time, she then had definite symptoms of hypothyroidism, so when she turned up with this anemia she was on the hypothyroid side. As I look at the blood counts, however, it seems possible that she was beginning her anemia while she was still thyrotoxic, but that the full-blown picture did not develop until she had swung down to a hypothyroid level. What all this means, I have not the faintest idea. I don't know that it means anything, but those are the facts and they are of interest.

I should like to ask Dr. Richardson about the occurrence of pernicious anemia in women of this age. Would it be some special kind of pernicious anemia since she is so young? Or would you accept it as classical?

DR. RICHARDSON: I would accept it as classical, because I don't see any other cause for it.

DR. MEANS: What is the youngest age at which you see classical pernicious anemia?

DR. RICHARDSON: This is extreme in my experience. I have two of this age. We get quite a few around 30, women and men.

DR. MEANS: We thought it was very young for classical pernicious anemia, and for that reason wondered whether any of this hypothyroidism or the preceding hyperthyroidism in this case might have played a role. Have you any idea?

DR. RICHARDSON: I wondered about it too, but I don't know. I think you could argue either way. I think 21 or adult life, is the only limiting criterion for pernicious anemia. I would say it does not occur in children or infants or even adolescents, so far as the pediatricians tell me, although there may be anemias which are relieved by liver in these age groups.

DR. MEANS: Well, you defined pernicious anemia as one which was relieved by liver, so you are getting into a little jam there.

DR. RICHARDSON: I am very much in a jam, that is true, but I am not sure that type is relieved by fraction G specifically. I did leave a little loophole. I mean to say that the diagnosis of pernicious anemia from the blood smear depends on one finding, and one finding alone, true, large, oval macrocytes, and they may be the only change in the blood picture. And the text book teaching is very wrong nowadays in that respect, unless it has been wisely revised, because it emphasizes the presence of megaloblasts in order to make a diagnosis, where the diagnosis should be made on clinical grounds plus the presence of true, oval macrocytes.

#### *Editor's Follow-up Note*

This patient was discharged on the 24th of February at which time she was subjectively well with a hemoglobin of 7.5 Gm. and a red blood cell count of 2.95 million. She was discharged on 15 units of concentrated liver extract weekly and was to return to the Medical Outpatient Department for follow-up studies.

#### CASE 16

##### MYOCARDIAL INFARCTION WITH MERCURY POISONING

DR. ROBERT S. PALMER: This morning we have a patient who is very difficult for me to diagnose and very difficult to treat. We would like your help. We

also have Dr. Harry A. Derow from the Beth Israel Hospital who knows about his past history and knows the details of one of the familiar diuretics which he has been using.

DR. FREDERICK S. BIGELOW: This patient, Mr. B., No. 562804, is 58 years old and was apparently in good health until 1943, when he had a myocardial infarction which brought him to the Beth Israel Hospital and resulted in a left bundle branch block. He recovered from his acute episode but thereafter had recurrent congestive failure such that he was admitted several times to the Beth Israel Hospital in a moribund state requiring thoracenteses and general measures of resuscitation. This continued despite digitalis, despite ammonium chloride, and mercupurin injections by vein. However, about four months ago he began a regimen not only of the use of digitalis but also of mercupurin or mercuxanthine pills by mouth, taking three such pills a day, each pill apparently being equivalent to about 30 mg. of mercury, so that during the course of each day he received about 0.1 Gm. of mercury. He continued also on ammonium chloride and diet, and on this regimen was improved very markedly, so that his chronic congestive failure disappeared entirely, he became asymptomatic and was able to be up and about, with no complaints.

He was followed regularly in the Beth Israel Outpatient Department and did well until the 28th day of January, 1947, when an albuminuria was discovered. Previous to that, many urinalyses as well as blood pressure determinations had been entirely normal. He continued taking his medicine until the onset of a stomach ache on about the first of February. This stomach ache continued, was localized about the umbilicus, and during the succeeding three days he felt increasingly weak, fell to the floor several times in trying to walk around the room and was eventually seen by his physician who found that the blood pressure was extremely low and therefore sent the patient to the hospital.

He was admitted to our Emergency Ward on February 3, 1947 in shock with an unobtainable blood pressure and with a chief complaint of pain in the abdomen in the region of the umbilicus. Up to the time of entry, he has been passing his urine successfully and having normal bowel movements.

On his entry here, we did not know what was wrong with him, but treated him for shock with plasma, with the result that by the morning after entry he appeared essentially normal with a blood pressure of about 110/80; his abdominal pain had disappeared. He had no edema at this time and his lungs were dry. His electrocardiogram showed left bundle branch block; whether it was recent or old we did not know. Shortly

TABLE 1  
*Blood Chemistry*

DATE	NPN (mg. %)	CL (m. eq./l.)	NA (m. eq./l.)	CO <sub>2</sub> (m. eq./l.)	K (m. eq./l.)	PROT. (A/G)	CA (mg. %)	P (mg. %)	CHOLEST. (mg. %)	CHOLEST. ESTERS
February										
4	90	87			4	1.2				
5			128	30						
7	45	95	128	34	3					
10	58	89	125	32		3.3				
13	60	95	131	32	2.2		8.8	4.0		
17, 18		93	127		2.8	3.4			624	30%

after entry, he had three days of bloody diarrhea, which then ceased and has not recurred. His blood pressures for the first 12 hours in the hospital and since that time have been of continuing concern. They have been low with a maximum in the range of 100/60 and a minimum of about 60/0, and he has been going into shock about every 24 hours since he has been here.

After about three days in the hospital, we began to think we knew a little more about what was wrong with him in the light of information about the mercu-xanthine which he had had by mouth, associated with the abdominal pain, the albuminuria, plus the bloody diarrhea. He, therefore, was treated with British Anti-Lewisite for three days and subsequently his course has been that of protein and electrolytic imbalance, which we have been trying to deal with from day to day. As I said, he did not have any edema when he came in here on the 4th of February, but edema began to appear in the sacrum and progressed to the legs, abdomen, and the right thorax. However, his lungs have continued relatively clear, with only a few râles from time to time at the right base.

Some of his blood studies are here in Table 1, but not by any means all of them. On the day of entry he had azotemia with chloride and potassium about normal, an extremely low total protein, but with albumin-globulin ratio of about 1.2. Since his entry his NPN declined temporarily to a low point of 44 mg. per cent, which is not shown and then increased again. His highest NPN was 90 mg. per cent. His chlorides on the whole have been low throughout, with a maximum figure of 95 m.eq./l. on the 13th of February and the sodium values have also run low throughout. His blood potassium, starting at normal has diminished on the whole to the region of 2.5 to 2.8 m.eq./l. His proteins have on the whole stayed fairly constant, although very low. At the time he came in he was extremely dehydrated so that his hemoglobin was in the region of 20 Gm. per cent, although even at that figure his proteins were low. Since then his hemoglobin has

TABLE 2  
*Diet*

DATE	PROTEIN	NaCl
February		
4-9	75 Gm.	1.5 Gm.
10-18	130	11
18-20	130	3-4
Blood Volume		6820 cc.
Plasma Volume		3385 cc.
Extracellular Fluid		28,200 cc.
Intracellular Fluid		24,815 cc.

declined to 16 Gm. with a hematocrit of about 40 on the 16th of February. His cholesterol two days ago was 624 mg. per cent with the esters being 30 per cent.

We have been treating this man with fluids and by diet. Initially his diet from the period of the 4th to the 9th of the month was a moderately low sodium, cardiac diet, which entails about 75 Gm. protein and 1.5 to 2 Gm. of sodium chloride per day. On or about the 9th of February we began to feel that probably he was losing not only protein in his urine, which we knew anyway, but also a good many electrolytes, such as sodium chloride and potassium, and therefore it was decided to increase his protein intake and also his sodium chloride intake. Therefore, he was put on a high protein diet with about 130 Gm. a day of protein and 11 Gm. of sodium chloride in total. This has been continued except that his sodium chloride was reduced to 3 to 4 Gm. two days ago. He has been able to eat throughout his hospital stay.

His urine findings are also shown in Table 3. Not only does he have large quantities of protein in his urine, with a maximum of 75 Gm. in 24 hours, but also 10 to 15 white cells and rare red cells with granular and hyaline casts. The figures on the urine chart have been converted from familiar equivalents to grams, principally as an aid in visualizing his intake in grams of sodium chloride.

Yesterday a urea clearance was performed which re-

TABLE 3

## Urine

DATE	PROT. (Gm.)	CL (Gm.)	K (Gm.)	NA (Gm.)	VOLUME (cc.)
February					
11	54	1.8			1400
12	75	0.8	3.5	.03	600
13	50	1.7	2.7	1.3	2500
15	45	0.6	2.5	.05	500
16	47	0.7	2.6	.04	1100
17	51	1.0	3.5	0.0	900
18	49	0.9	3.0	.01	1500
19		Urea Clearance		26%	1300

vealed 26 per cent of normal clearance and in addition, determinations of fluid volumes were performed, which showed a blood volume of 6,820 cc., plasma volume of 3,385 cc., his extracellular fluid being 28,200 cc. and intracellular fluid 24,815 cc.

In the attempts to maintain this man's body proteins not only by diet, he has also had plasma given to him and so far has had 5,200 cc. of plasma and 1,000 cc. of whole blood. On the whole he has been getting some quantity of either plasma or whole blood each day. Initially we gave him Red Cross plasma, until we became aware of the mercury content of the preservative in it, and have since then switched to the Massachusetts General wet plasma, which is for burn patients. Nevertheless we do not seem to be keeping up with his protein by any means.

DR. PALMER: Unhappily, in the two weeks and one day that Mr. B. has been with us, he seems no better, although we hope we are more informed about him. He is too sick to be brought over for you to see. He is in bed and he can lie flat. He is very pale in appearance, and he has very extensive edema of the legs and of the abdominal wall. We believe he has ascites. At one time we wondered if he did not have an amount of fluid in the pericardium which might be tapped. He had a large, quiet heart, very poor sounds, and the appearance by x-ray in a somewhat rotated plate suggested fluid, but the x-ray department did not feel that there was a significant amount. He has some edema of his arms, but of course, he has had a great many intravenous fluids.

When he first came in, before we knew the details of his blood chemistries, I suggested the possibility of coronary occlusion since he had severe pain, even though abdominal, had known coronary disease, and was in severe shock. Dr. Derow tells us that there is no additional change in our recent electrocardiograms. There is nothing in our tracings to indicate a fresh occlusion. Next, as more information about him appeared, I thought that he had had congestive failure,

then a prolonged diuresis, and that he was simply suffering from protein and sodium or other electrolyte starvation. The more we considered the effect of the mercurial diuretic, the more apparent the "working diagnosis" became, namely, chronic mercury poisoning with mercurial nephrosis, complicated by congestive failure. Where some of these electrolytes go, I don't know, since excretion studies do not account for the total loss. Perhaps we have lost them in his edema fluid rather than via the urine.

Before we hear from Dr. Derow about this patient, we would like to ask Dr. Allan Butler to comment.

DR. ALLAN M. BUTLER: A patient who has congestive cardiac failure, low serum protein, edema, and renal insufficiency is difficult to care for. The specific gravity of his urine is said to be about 1.025. With gross albuminuria, that specific gravity does not give you any idea as to what the concentrating ability of the kidneys is. And with this much edema, I don't know any way of appraising this patient's renal function without doing such a test as a urea clearance. In circumstances like this, urea clearance is probably the most convenient way of appraising renal function. What has his weight change been since he has been in the hospital?

DR. BIGELOW: He has been putting on weight. We haven't weighed him since the gross edema appeared.

DR. BUTLER: He has been putting on weight. In children we are not confronted with the treatment of cardiac failure to the same extent as you are in adults, but as pediatricians we watch the treatment of adults with mercury diuretics who have cardiac failure and a very poor urine output and some cardiovascular renal disease and wonder how often the temporary beneficial effect of diuresis is followed by a deleterious effect on the individual's renal function and an accelerated renal failure. This patient perhaps provides the occasion for so wondering.

The data indicate that his extracellular fluid and plasma volume are huge. One of the limitations of these measurements is that you need them in patients where the conditions result in large errors, and I have no idea how accurate these measurements are. The plasma volume is almost certainly too big, due to the fact that the serum protein is seeping out of the plasma into the extracellular edema and into the urine at a great rate, because the dye goes where plasma protein goes. But it is unfortunate that in the very patient in whom you wish to measure plasma volume and extracellular volume most methods contain the greatest error and therefore provide the least information.

From the data available it looks as though ammo-



nium chloride might be an effective diuretic. If the degree of the acidosis produced is watched carefully, I can see no harm in trying it and believe it should be tried before giving acacia.

DR. PALMER: Dr. Derow from the Beth Israel Hospital has been interested in this diuretic which Mr. B. has had. Will you tell us about that and comment on Mr. B.'s situation?

DR. HARRY A. DEROW: Since Mr. B.'s admission to the hospital, I have seen him on two occasions. I have been impressed with several features of his clinical course. In the first place, he has prevented the picture of shock with hypochloremia and hypoproteinemia. The marked chloride loss and hypoproteinemia are probably related to the increased permeability of the capillaries because the patient suffered a very brief episode of diarrhea but did not vomit at any time. Peters\* in 1933 pointed out the important fact that in mercury poisoning a condition develops resembling surgical shock with marked disturbances in the electrolyte equilibrium. He further stated that the electrolyte patterns in the fatal cases are characterized by progressively falling serum proteins, low bicarbonate, chloride and base, with phosphate usually elevated. None of Peters' patients showed the severe degree of shock and electrolyte disturbances as long as Mr. B.

In the second place, the blood cholesterol of 624 mg. per cent is very striking and may be related to the marked degree of albuminuria and hypoproteinemia. We are dealing now with what appears to be a nephrotic state characterized by generalized anasarca, hypoproteinemia, hypercholesterolemia, and massive albuminuria. As a result of the shock-state, the transudation of the proteins into the tissues due to the increased permeability of the vessel walls may play an important role in the pathogenesis of the hypoproteinemia and anasarca. The latter has been very resistant to treatment with blood and plasma transfusions and it is possible that spontaneous diuresis may occur with disappearance of the edema.

In the third place, the disappearance of the congestive heart failure has been striking. This patient prior to the institution of oral mercupurin therapy had been receiving for a period of at least one and a half years weekly or semiweekly intramuscular injections of mercupurin in addition to very frequent thoracentesis. One now sees him perfectly comfortable, flat in bed, without any shortness of breath in spite of the massive generalized anasarca.

DR. PAUL D. WHITE: Has he been on a very low

sodium intake throughout this period, do you recall?

DR. DEROW: We have had him on a low salt diet.

DR. WHITE: Not extremely low?

DR. DEROW: Not extremely low. He has not used the salt shaker and the foods which were prepared for cooking were on the low sodium chloride side. But he must have been getting from 2 to perhaps 4 or 5 Gm. of sodium chloride on his diet per 24 hours.

DR. BUTLER: Is he getting any ammonium chloride?

DR. BIGELOW: No, sir.

DR. BUTLER: What is his fluid intake?

DR. BIGELOW: The fluid intake runs around 2,000 cc.

DR. BUTLER: Have you tried getting it up?

DR. BIGELOW: He gets it ad lib essentially now. We have not forced it.

DR. BUTLER: Would Dr. White be interested in forcing it in such a patient?

DR. WHITE: I think it might be worth a gamble.

DR. CONGER WILLIAMS: What about a trial of acacia? We have had fair luck with two patients with the nephrotic syndrome or the nephrotic state of chronic nephritis in whom the ordinary protein has not worked but acacia did.

DR. WHITE: Dr. Derow, you have used mercurial diuretic by mouth for some time in a good many patients, haven't you?

DR. DEROW: Yes. There is another interesting feature in this patient which does not seem to fit in with the patients in Dr. Peters' group, for instance. To explain this marked loss of chloride and protein is difficult. This man has not been vomiting and has had a very brief period of diarrhea, so that we cannot explain these marked losses on those two bases. We are left with the possible explanation that as part of the shock picture this man's capillaries became increasingly permeable, so that it was possible for the protein and chloride to leak into his tissue spaces rather than explaining it on the basis of diarrhea and vomiting which are very frequent problems of mercury poisoning.

DR. WHITE: Do you think the BAL may have stopped some of that? He had it for three days.

DR. DEROW: Well, Dr. White, the dose of mercury that you give a patient is not cumulative if the patient's urinary volume is maintained at a fairly high output. So that while shortly after he got here the urinary test for mercury was positive, I don't know what subsequent tests showed.

DR. BIGELOW: There were about three such tests done daily that were positive and they then became negative.

DR. DEROW: So that after a period of time there no longer is any testable mercury in the urine and even

\* Peters, J. P., A. J. Eisenman, and D. M. Rydd: Mercury poisoning, *Am. J. Med. Sc.*, 185:149-162 (Feb.) 1933.

in the feces, although there may still be some in the viscera.

DR. JOSEPH C. AUB: You mean to say the mercury in the urine disappears after three days.

DR. DEROW: Testable mercury, mercury that will be revealed by chemical testing.

DR. AUB: It depends upon how accurate your testing is, because a good deal of mercury stays in the bones and other tissues thereafter and it must gradually come out, I should think.

DR. DEROW: The suggestion to use acacia is sound since we must continue to try to increase the colloid osmotic pressure of the blood in order to return to the blood vessels the fluid and salt that comprise the edema. Perhaps in this case, the capillary damage is irreversible so that because of the permeability of the capillaries, the use of acacia and similar colloids may be ineffective. However, in view of the desperate condition of the patient, I think that acacia should be tried.

I have been asked to report our study of the efficacy and safety of mercupurin tablets orally administered to eleven ambulatory patients with chronic congestive heart failure.<sup>†</sup> Each tablet contains 120 mg. mercupurin, or 30 mg. mercury and 27 mg. anhydrous theophylline, and is the equivalent of 0.88 cc. of the parenteral solution of mercupurin. All the patients received ammonium chloride and a maintenance dosage of digitalis each day, and followed a low salt diet.

On the basis of our studies, it is apparent that individualization of the method of administration and dosage of the oral mercupurin tablets is necessary to obtain satisfactory results. The schedules we have used satisfactorily, include giving one to three tablets daily, two to three tablets five consecutive days each week, three tablets every other morning before breakfast, and two tablets every other evening at bedtime.

The results were uniformly excellent.

In spite of the most meticulous care, recurrence of congestive heart failure occurred in this group of patients and was due to discontinuance of the tablets, respiratory infections, and paroxysmal rapid heart action. These recurrences were handled satisfactorily by giving one or two injections of mercupurin at weekly intervals with the continuance of the oral mercupurin tablets.

There were no toxic manifestations in five patients on various dosage schedules for from 7 to 26 months. At each visit we examined the patients for signs and symptoms of congestive heart failure and mercurial-

ism. In six patients toxic manifestations appeared. Four patients had cramps and/or diarrhea; one patient had anorexia and nausea; one patient had soreness of the abdomen; one patient had gingivitis; and one patient, Mr. B., acute mercurialism. In retrospect, the development of acute mercurialism in Mr. B. was due to inadequate supervision. This patient had been on oral mercupurin therapy for four and a half months, during which period he was free from signs and symptoms of congestive heart failure and showed repeatedly negative urines. One week before the symptoms of mercurialism appeared, a urine examination showed four plus albumin. Unfortunately, this finding was not reported to us and the drug was continued the following week, at the end of which time he developed the picture of shock and so forth.

In summary, oral mercupurin therapy is an important adjunct in the treatment of chronic congestive heart failure. Satisfactory results are obtained only if the scheme of dosage and administration of the drug is individualized. Toxic manifestations of minor degree occur in some patients but do not interfere with continuance of treatment. The instance of severe mercurialism which we observed makes it necessary to stress the importance of adequate supervision of patients receiving this drug.

In conclusion, I would like to discuss briefly the management of the minor toxic manifestations. Most of the gastro-intestinal toxic manifestations occur within one to three or four weeks after the institution of the tablet therapy. In some instances, in spite of the continued usage of the drug, these gastro-intestinal complaints disappear. In other instances after we discontinued the drug for variable periods of time, the symptoms disappeared, and thereafter the drug was reinstituted without development of toxic manifestations. In none of the patients with gastro-intestinal complaints was albumin found in the urine; one patient who suffered with severe pyorrhea before the drug was begun developed gingivitis after two weeks of the drug. After the drug was omitted for a week, the gums returned to their previous unhealthy state and the patient failed to develop a recurrence of the gingivitis when the drug was resumed. The gingivitis did not appear again, in spite of the continued use of the drug, until one year later. The drug was omitted, the gingivitis disappeared, and some time later, after the drug had been resumed, he again developed gingivitis, which again disappeared after the drug was omitted. These minor toxic manifestations present no serious problem in management.

DR. PALMER: Thank you, Dr. Derow, for giving us

<sup>†</sup>Derow, H. A., and L. Wolff: Oral administration of mercupurin tablets in ambulatory patients with chronic congestive heart failure. To be published.

the details of this. It reminds us that perhaps any diuretic except water as Dr. Butler suggests is dangerous. I remember using salyrgan in hypertensive patients without failure in studying the concentration of the urine, and we noticed then in some 30 cases that those without urinary changes of significance commonly showed albumin or increased albumin and red cells. And so with this one, perhaps, water is the thing to give. Perhaps the edema is sometimes compensatory, even as it is in heart failure. Perhaps if he continues to swell up he would be a suitable person for acacia. In the matter of the mercury, on the third day here, he had a plus or minus Rausch test, the Army test for mercury, and the Gettler test was positive and by the 16th and 17th of February, which was his 12th hospital day, the mercury test was negative.

DR. WHITE: It may be that you might be able to halve the dose of mercury or even reduce it more on a stricter sodium intake. We ourselves have been able to do away entirely with mercurial diuretic parentally in a good many cases by such a change to a very low sodium diet. It does help to cut down the amount of mercury needed.

#### *Editor's Follow-up Note*

After this patient was presented on the 20th of February 1947 his course was that of steady progressive deterioration despite transfusion, a full course of acacia, and the usual supportive measures. His edema increased gradually and finally toward the end he had massive anasarca. He died on the 7th of March 1947. Postmortem examination was refused.

#### CASE 17

##### GASTRO-INTESTINAL BLEEDING

DR. ROBERT S. PALMER: This problem is a gastro-intestinal one, persistent severe bleeding in a young adult. Mr. C. is 22 years old.

DR. JAMES H. AVERILL: Mr. C., No. 147933, a 22-year-old, white male, came to the hospital on February 9, 1947 because of a massive gastro-intestinal hemorrhage. He had been well until 1942 at which time while working in a local store as a clerk he became weak, tired, dizzy, and noted palpitation of the heart. He went to the clinic in the store and was found to be anemic. He was referred to an outside hospital where he was found to have splenomegaly and microcytic hypochromic anemia. He was x-rayed from stern to stern. A gastroscopy and sigmoidoscopy failed to reveal any cause for the bleeding. He was discharged at the end of two weeks after being treated with iron and liver with a diagnosis of microcytic hypochromic anemia. He attended the Outpatient Department of

that hospital for five months and then because he felt so well he discontinued his visits.

In April 1943 he again had weakness and palpitation, became pale, and re-entered the same hospital. This time they found x-ray signs of an old duodenal ulcer. He was treated for that and discharged at the end of three weeks quite well. His last visit to that hospital was in August 1943. He did fairly well until December 1944 when he had right lower quadrant pain and had an appendectomy done uneventfully at another hospital. He next got into trouble in June 1946 when he had a recurrence of weakness, without any abdominal distress whatsoever. He never had had hematemesis and never prior to last June had black stools.

He came into the Emergency Ward at this hospital in June 1946 where he was found to be quite pale and had a hemoglobin of 6 Gm. with 1,500,000 red blood cells. He was admitted to the House where he was studied thoroughly. Various questions were raised because of the painless nature of his bleeding. He had a gastro-intestinal series done which again showed a questionable old duodenal ulcer but no crater was seen, nor has it ever been seen. He had a barium enema and small bowel series which were all negative. He received a number of transfusions following which he did well. He was discharged with a diagnosis of ulcer. He was followed carefully in the Outpatient Department and stuck very carefully to an adequate ulcer regimen.

On February 9, 1947 he re-entered because of weakness, dizziness, and tarry stools. We have studied him completely again. We think we have found an old scarred ulcer in the duodenum but no ulcer crater. We have treated him with nine blood transfusions and diet to which he has responded well. He now feels perfectly well and he has 13 Gm. of hemoglobin.

We present the problem of a young man of 22 who has bled severely and painlessly four times. We are faced with a problem in therapy and diagnosis.

DR. PALMER: One question for Dr. Robbins is whether there is positive x-ray evidence of ulcer? From the x-ray point of view is this lesion enough to account for the bleeding? I think it fair to say that he has not had too much distress or pain throughout his illness. The history is chiefly one of recurrent bleeding and not distress.

DR. LAURENCE L. ROBBINS: From some of these films alone it seems pretty definite that he has a deformity of the duodenal cap which is certainly characteristic of the previous ulceration. I see nothing that indicates an active crater, however. There are some spot films that show the esophagus. There is no evidence of varices. There is some thickening of the mucosa

of the stomach. However, we do not see the crater which would explain the bleeding. One thing that should be pointed out is that with this much deformity of the duodenal cap one can have an active crater which will not be seen.

DR. PALMER: We then have more than a presumptive diagnosis of duodenal ulcer. We have a young man with excessive bleeding. Certain questions in regard to therapy have been raised. The last medical treatment, considered by some to be adequate, has consisted of frequent alimentation only. I believe frequent alimentation is important, perhaps most important; I am still persuaded that a low residue diet is important also and I believe the use of atropine in full doses is important as well.

Vagotomy is still a new procedure which is not seasoned and patients have not been followed long enough to be certain of its effects and I suspect this patient is not suitable for that procedure. Finally there is a question of exploration and possible subtotal gastrectomy. I would like to ask Dr. Bock who I know is interested in this problem for his opinion.

DR. ARLIE V. BOCK: This is an unusual case of a history of a duodenal ulcer without accompanying pain. It is an atypical case. I would doubt very much whether the diagnosis is really duodenal ulcer. I would want him explored to see if he has anything like leiomyosarcoma.

DR. CHESTER M. JONES: At Gastro-intestinal Rounds yesterday we felt the same way. The complaint has not been pain. Therefore we doubt the diagnosis.

He ought to be explored to find out the cause. One other possibility would be Meckel's diverticulum which can give you bleeding as severe as this. It is difficult to demonstrate by x-ray. We have not been able to show it very often, have we, Dr. Robbins? It is quite uncommon. It is almost impossible to ask an x-ray man to do such a thing.

There are benign tumors without pain. If on exploration nothing is found, then it would seem to me that the evidence of an old ulcer scar would be sufficient to go ahead and do a subtotal gastrectomy without any question at all. The duodenal cap would be the last place to look.

DR. JAMES H. MEANS: We had one case where radiology could not demonstrate varices.

DR. JONES: He might have varices of the stomach.

DR. MEANS: They were in the stomach and not demonstrated. Dr. Benedict, I think, had to demonstrate them by gastroscopy.

DR. JONES: We have had several of those.

DR. MEANS: I was wondering if there were more diagnostic studies that could be made.

DR. JONES: He has been gastroscoped elsewhere. That was negative.

DR. MEANS: What about the small bowel?

DR. JONES: That has been done.

DR. MAURICE FREMONT-SMITH: Is the spleen enlarged?

DR. AVERILL: Not at present.

DR. EARLE CHAPMAN: I have just been through a problem of this kind which after three years was successfully terminated. I explored the same problem of painless bleeding in a man somewhat older. We had the same thoughts in mind as Dr. Bock, and Dr. Arthur Allen explored the man, without finding a cause for the bleeding. He was closed up and was allowed to go home on an ulcer regimen. He bled again, and Dr. Claude Welch saw him and said that he believed the man was bleeding from a shallow ulcer near a superficial vessel in his duodenum. He said we should do a resection on the duodenum without any previous diagnostic studies and look at it carefully when opened. We did this, and sure enough, there was the origin of his bleeding. Pathologic specimens disclosed superficial ulcer in the duodenum from which he was bleeding. It has ended the problem.

I think your patient is similar to mine. I would predict that if he were resected a similar cause for the bleeding would be found.

DR. JONES: It could be.

DR. PALMER: The program then will be a careful exploration followed by resection if nothing more is found.

### *Editor's Follow-up Note*

The day after this patient was presented at Grand Rounds he again had a bout of gastro-intestinal hemorrhage which resulted in symptoms and signs of mild shock. By the use of whole blood transfusions his condition improved, but on the 8th of March after repeated consultations with the Surgical Service it was decided that he should have an exploratory laparotomy without further ado. At this time a hemangioma of the jejunum was found and 10 cm. of bowel were resected and an end-to-end anastomosis performed. On pathologic examination the hemangioma measured  $5.5 \times 5 \times 1.5$  cm., involved about three-fourths of the bowel circumference, and bulged into the lumen to about 1 cm. distance. His postoperative course was uncomplicated and he was discharged on the 17th of March 1947 on a six-meal bland diet, with the expectation that he would have no further trouble.

# Clinicopathologic Conference\*

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This 51-year-old white male was admitted to the Medicine Service of the John Gaston Hospital, May 31, 1946. He stated that for the past six months he had experienced general malaise with occasional nausea and vomiting following meals. There was no particular food dyscrasia. Some six weeks before admission he began to have chills, followed by fever, approximately every second night at about 9:00 to 10:00 P.M. The onset of chills was followed by a dull pain in the right costovertebral area with radiation to the epigastrium. The pain was aggravated by twisting the body. Slight dysuria and nocturia of five to six times nightly were said to have been present since the onset of the chills. Patient received treatment from a private physician for "pus on the kidneys," but obtained only temporary relief. The chills, fever, and pain had decreased in severity during the ten to fourteen days prior to admission. These episodes were said to be definitely different from malaria chills which the patient had experienced some seven to eight years previously. He had lost approximately 30 to 35 pounds in body weight in the past six months before admission. He lived on a farm, drank unpasteurized milk, and obtained water from a deep well which was located on a hillside above the family latrine.

A review of the patient's past history revealed only an acute anterior urethritis some 25 years previously, and a chronic cough with production of small amounts of mucoid sputum for the past five to ten years.

## Physical Examination

**GENERAL:** A well-developed, fairly well-nourished white male in no apparent distress, but with the ap-

pearance of some weight loss. The temperature was 101° F., pulse 80, respiration 20, and the blood pressure 120/80.

**TONGUE:** Heavily coated with a light brown fur.

**TEETH:** Markedly carious.

**CHEST:** Slight prominence of the right lower lateral chest with moderate pain on deep palpation over this area. The excursion of the diaphragm was normal. Inspiratory squeaks and a few dry râles were present throughout the lung fields.

**ABDOMEN:** Liver and spleen were not palpable.

The remainder of the physical examination was negative.

## Laboratory Findings

**Blood:** The red blood count was 4,000,000, hemoglobin 9.5 Gm. per cent, and the white blood count was 10,000.

**Differential:** N. metamyelocytes 1 per cent, N. nonfilamented 4 per cent, N. filamented 76 per cent, eosinophils 5 per cent, basophils 1 per cent, lymphocytes 12 per cent, and monocytes 1 per cent.

**Kahn Test:** Negative.

**Nonprotein Nitrogen:** 33 mg. per cent.

**Sedimentation Rate:** 15 min.—26 mm.

30 min.—30 mm.

45 min.—31 mm.

60 min.—31 mm.

**URINE:** Specific gravity 1.015; albumin, negative; microscopic examination, 3 to 6 WBC/HPF in the centrifuged specimen.

**STOOL EXAMINATIONS** for parasites were done on four occasions. The initial moist preparation of a formed stool was reported questionably positive for *E. histolytica* cysts by the student, but the finding could not be confirmed with a special iron-hematoxin preparation. Two purged stools were negative.

**MALARIA SMEAR:** Negative.

\* Presented at the Regional Meeting of the American College of Physicians, Memphis, Tenn., by the Departments of Medicine, Radiology and Pathology, University of Tennessee Medical School.

AGGLUTINATION SERIES for typhoid, tularemia, brucellosis, and proteus X-19, negative on two occasions.

CEPHALIN CHOLESTEROL FLOCCULATION: 3 plus at 24 and 4 plus at 48 hours, and on repeated examination was negative at 24 and 48 hours.

BLOOD CULTURE for pyogens and typhoid bacilli, negative.

STOOL CULTURE for typhoid, paratyphoid, dysenteriae organisms, negative.

BROMSULFALEIN TEST (5 mg./Kg. body weight): 8 per cent retention in 45 minutes (test done 11th hospital day).

GASTRIC WASHINGS: Negative for tubercle bacilli.

X-RAY of chest was negative on admission.

### Hospital Course

The patient had a chill on the night of admission, and his temperature ranged up to 104° F. the first two days. Following this he had an intermittent type fever with daily elevations to 102° F. On the sixth hospital day the chest pain had increased, and the prominence in the posterolateral region of the right lower chest was more pronounced. The diaphragm was again found to move well on forced respiration. Two days later the pain was quite severe, and was accentuated by respiration. Tactile fremitus and breath sounds were markedly diminished over the right lung base posteriorly, and the right side of the diaphragm moved only slightly. Fluoroscopic examination confirmed the marked limitation in motion of the right side of the diaphragm, and showed minimal congestive changes in the base of the right lung.

Emetine hydrochloride was given in doses of 1 gr. intramuscularly daily, and five days later Carbarsone was begun in doses of 0.25 Gm. twice daily. Each was continued for ten days. During this therapy, there was only slight decrease in the fever.

On the 18th hospital day, 200 cc. of yellowish pus, streaked with a small amount of blood and dark brown material, was aspirated through the right tenth intercostal space medial to the scapular line. Microscopic examination of a moist preparation of the fluid revealed many pus cells and red blood cells, but no amebae. Culture revealed *Strep. fecalis*, *B. coli*, and *B. aerogenes*. Following the aspiration, there was marked symptomatic improvement. The temperature fell to normal, and the white blood cell count dropped to 7,200. X-ray studies of the upper gastrointestinal tract and the colon were done and reported negative.

On the 24th hospital day, the temperature began to rise again, and became intermittent with daily elevations to 102° or 103° F. The pain and bulging of the

right lower posterior chest also returned. A second liver aspiration was done on the 33rd hospital day with the removal of 250 cc. of very thick reddish pus. Air was injected into the abscess cavity, and x-ray examination revealed a multilocular area of decreased density located posteriorly in the region of the right lobe of the liver. The aspirated fluid contained many red blood cells and much debris. Culture was positive for *B. aerogenes*.

There was only slight improvement following this aspiration, and the patient was transferred to the Surgery Service for open drainage. Treatment consisted of resection of the right 12th rib with open drainage of the abscess cavity, sulfadiazine, penicillin, and general supportive measures including multiple blood transfusions. There was some symptomatic improvement, although intermittent fever continued with elevations to 101° or 102° F. daily. Six weeks after the first operation, the temperature had risen to 103° F. daily, and a second operation was performed. A walled-off abscess was found in the substance of the liver, and a defect was noted in the diaphragm with extension of a sinus tract into the right pleural space.

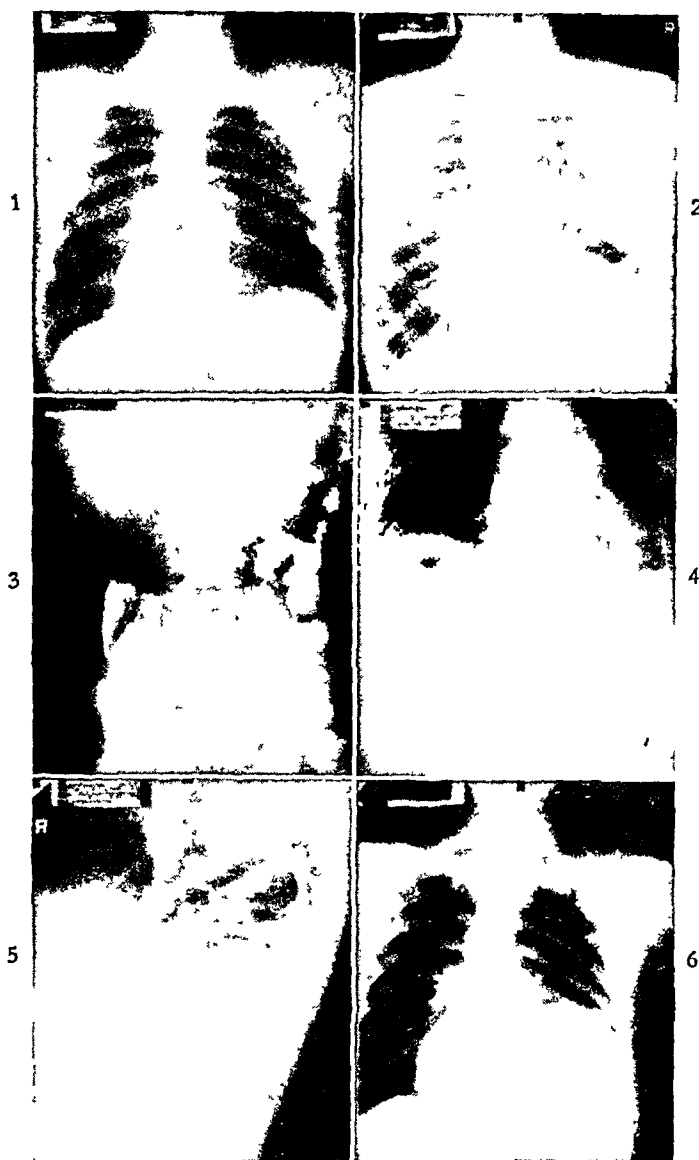
Following this operation, there was some decrease in the fever. The general condition of the patient deteriorated with fall of the total plasma protein to 5.5 Gm. per cent and red blood count to 2,500,000 with 9 Gm. of hemoglobin in spite of repeated blood transfusions. By the 114th hospital day, some 23 days after the second operation, the condition was critical, and x-ray examination revealed infiltration with multiple areas of decreased density in the right lung field. A third operation was performed with resection of additional ribs and drainage of the lung abscesses. The course was rapidly downhill, and the patient expired on the 119th hospital day.

### RADIOLOGIC DISCUSSION

DR. J. M. DOUGALL: Selected films are presented. The first chest film (Fig. 1) is negative, that is, it is compatible with the average chest film; however, fluoroscopic study demonstrated a splinted diaphragm, especially about the periphery.

Several days later a second study (Fig. 2) was carried out. The changes were more pronounced and the right side of the diaphragm was definitely elevated. On both examinations subphrenic or liver abscesses were suspected.

Gastro-intestinal examination, including barium enema, did not show any lesion (Fig. 3). The only suspicious finding was an irritable transverse colon.



FIGURES 1-6

An abscess cavity was aspirated by needle, and air injected. Films then showed a cavity thought to be in the liver (Fig. 4 and 5).

Later chest studies (Fig. 6) show a certain extension of this inflammatory process into the base of the right lung with abscess formation.

I believe this is amebic liver abscess with extension to the lung. Any subphrenic or liver abscess may involve the chest due to lymphatic drainage from the liver surface and diaphragm into chest; amebic abscess spreads by direct extension through diaphragm into chest. Usually no amebae are found in the aspirated pus and mixed infections are common.

#### CLINICAL DISCUSSION

DR. CONLEY H. SANFORD: This case is somewhat different from the usual type of conference cases in that

the diagnosis is obvious. The aspiration of purulent material from the region of the liver and subsequent surgical drainages of the liver abscess leave no room for speculation as to the diagnosis. It seems that our problem is to attempt to solve what type of abscess this patient was a victim of, and the source of the infection.

When one considers abscess of the liver, one immediately thinks of the *Endameba histolytica* as the causative organism. We should not be led too far astray by the failure to demonstrate these organisms in the stools because it is well known that in a considerable percentage of proved amebic abscesses repeated examinations of the stools have been negative. The character of the contents aspirated from the cavity was not that usually seen in amebic abscesses. The aspirated material was described as being yellowish, streaked with a small amount of blood. In amebic abscesses the contents are usually brownish-red, or the so-called "anchovy sauce material." The type of material found here is occasionally present, however, in amebic abscess, as a result of secondary infection. There is a lack of previous history in this case suggestive of amebic colitis as a forerunner of the abscess. It should be emphasized, however, that such previous histories are not infrequently absent in amebic abscesses of the liver. Perhaps one of the most convincing arguments against this being an amebic abscess is the failure of the patient to manifest any improvement at all following fairly intensive anti-amebic treatment. While amebic abscess cannot be definitely ruled out in this case neither can its diagnosis be definitely established, and it seems reasonable to doubt that this was an amebic abscess.

It would be of some help if we could determine whether this abscess was solitary or multiple. Solitary abscesses often begin as multiple ones and after breaking down coalesce to form one large abscess. Roentgenologic and surgical evidence would seem to indicate that this was a solitary abscess, or at least had become solitary by the time the diagnosis was made. Multiple abscesses are often acute at onset, and progress rapidly downward to a fatal termination.

Assuming that this was not an amebic abscess, one is concerned regarding the source of the infection. Abscesses in the liver occasionally occur as a result of a bacteremia. When this occurs, the abscesses are usually multiple and more often than not their occurrence is more or less a terminal event. Repeated blood cultures in this case were negative. There were no clinical evidences of bacteremia and I believe that this can be fairly definitely ruled out as a cause of the liver abscess in this case.

Pyogenic infection producing liver abscesses occasionally is carried by way of the portal vein. This follows appendicitis or infectious processes elsewhere in the region of the abdomen drained by the tributaries of the portal vein. This patient gave no evidence of having had such an infectious process prior to the appearance of the liver abscess. This route of infection usually gives rise to multiple abscesses, the onset is acute, and the course is rapid and fulminating.

Other sources of infection which apparently are not applicable in this case are by way of the hepatic artery, by way of the hepatic vein, by way of the bile ducts, extension from contiguous structures, trauma, and parasitic diseases.

References to the literature would indicate that authors have often been on about the same "spot" that I am in this case, and that in a number of instances they have never been able to find the source of infection even at necropsy. For want of a better term they have grouped these cases under the heading "primary idiopathic liver abscesses." I am afraid I shall have to put this case in such a category.

In a case of this kind one should think of the possibility of a cyst of the liver which has become infected. Polycystic disease of the liver occurs, but it is usually accompanied by cysts in the kidney, pancreas, lungs, spleen, or brain. We have no evidence of the existence of cysts in these organs in this case. Furthermore, if we adhere to the opinion that this cavity was solitary, it would best be explained on the basis of an infected solitary cyst.

Solitary cysts of the liver are usually found in patients 40 to 60 years old, in which age group this patient falls. They are much less commonly seen in men than women, however. They produce no symptoms unless they attain such size as to produce pressure on surrounding structures. Rupture and infection are the most frequent complications, and both these conditions occurred in our case.

Involvement of the lung is an expected sequence in hepatic abscess. As in this case, the involvement may be by direct extension through the diaphragm, but it should be borne in mind that penetration of the diaphragm is not necessary to lung involvement. The latter may occur by way of lymphatic drainage.

Attention may well be called to what appear to be some errors in therapeutics in this case. In a large abscess of the liver with pyogenic organisms present in the exudate adequate drainage is essential. Over three weeks elapsed after definite diagnosis by aspiration was made before surgical drainage was resorted to. The surgical treatment itself was apparently not effectively performed since the wound was undoubt-

edly allowed to close too early, and the abscess cavity again filled with pus necessitating subsequent operation. Even if the abscess were known to be amebic, surgical drainage should be resorted to when it has attained this size and when failure to respond to medical treatment has been observed. Without surgical drainage these large abscesses invariably rupture, as it did in this case, and it seems to me much better to control the direction of drainage by surgical intervention.

DIAGNOSIS: Primary idiopathic liver abscess  
Abscess of the lung, secondary  
Possibility of infected solitary cyst of liver

### PATHOLOGIC DISCUSSION

DR. DOUGLAS H. SPRUNT: As pointed out by Dr. Sanford it is obvious that this is a case of liver abscess. The etiologic diagnosis of amebic abscess was made at the time of the last surgical intervention on a biopsy of the liver. Numerous amebae were found in this specimen.

At necropsy a large multilocular abscess in the right lobe of the liver was found. This abscess measured approximately  $10 \times 15$  cm. It extended to the diaphragmatic surface and through the diaphragm to the right lower lobe of the lung. There were dense fibrous and fibrinous adhesions between the dia-



FIGURE 7



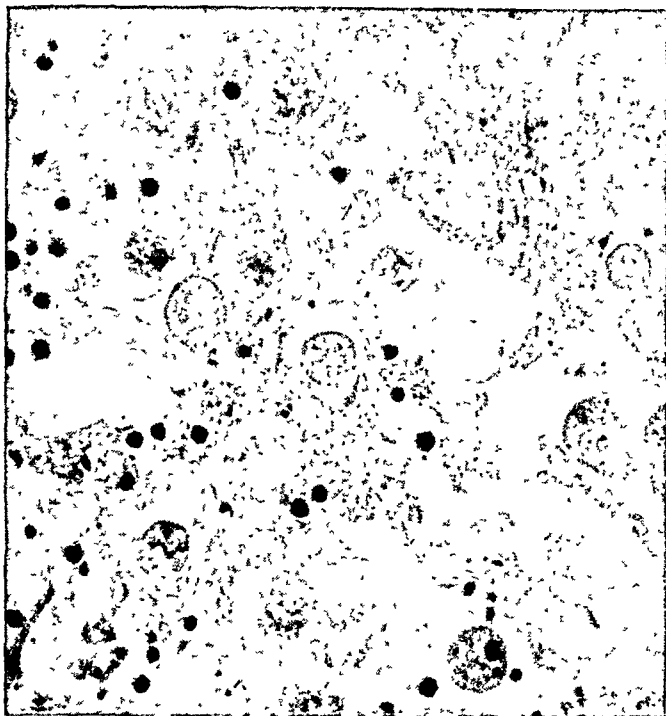


FIGURE 8

phragm and the liver. The right lung also contained numerous abscesses which took up practically all of the lower lobe. There was an intensive bronchopneumonia in the right lower lobe.

Microscopic preparations of the liver showed (Fig. 7 and 8) the center of the abscess to be composed of a pink-staining amorphous debris in which were numerous bacteria. No amebae were seen in the center of the abscesses. The walls of the abscesses showed a slight round-cell infiltration and a large number of amebae.

In the microscopic preparations of the lung abscesses similar to those found in the liver were visible. Numerous amebae were present. The surrounding lung tissue was collapsed and there were considerable amounts of fibrin but few cells. There were also patches of lung tissue containing large numbers of polymorphonuclear cells and some bacteria. Sections from the left lung showed a diffuse polymorphonuclear reaction. There were no abscesses and no amebae in this lung.

In the descending colon (Fig. 9) there were several ulcers. These ulcers were interesting in that the mucosa was missing over only a small area. These were not undermined and were apparently quite recent.



FIGURE 9

Numerous amebae were seen at the base of the ulcer and in the muscular coats of the intestine. Only a few lymphocytes and macrophages were seen.

There was an acute fibrinous peritonitis in the right upper quadrant of the abdomen and a number of old fibrous adhesions. The other organs were essentially negative. The brain was not examined.

The absence of amebae in the center of the liver abscess and their presence in the wall is typical of amebiasis of the liver and explains the failure to find the amebae in the aspirated material. The absence of cells in the liver, lung, and intestines is also, of course, characteristic of amebiasis. The only really unusual feature of the case and the one which caused the difficulty in diagnosis was the intestinal lesion. The ulcer here was apparently quite recent. Our explanation is that the primary intestinal lesion was quite small and that after the liver became infected the intestinal lesion subsided without leaving much damage. The lesions we found at necropsy were the result of a terminal reinfection from the liver.

# CASE REPORT

## The Differential Diagnosis of Acute Reflex Trismus and Tetanus, after Exodontia

JOHN L. SWITZER, M.D.

CHICAGO, ILLINOIS

Tetanus is well known to the laity as "lockjaw," and any process which causes a tightening of the jaws readily produces alarm, and in some instances, hysteria. It is most important that the practitioner realize that several oral diseases may produce trismus which superficially resembles the early stages of tetanus. Particularly is it serious if there has been prior injury and the physician is called upon to establish a diagnosis and begin therapy. To be unable to open one's jaws is terrifying and the physician must have the knowledge which enables him to cope with this problem both from a physical and a psychologic standpoint.

To have a complete understanding of trismus it is necessary to review the various causes which produce spasm of the masticating muscles.

Limited movement of the jaws may be acute or chronic. Chronic limitation is ankylosis and this may be true or false. In true ankylosis there are permanent joint changes. Permanent, or true ankylosis, may result from extension of middle ear disease to the mandibular joint, or from acute arthritis. It may also result from accidental joint injury with hemorrhage as from forceps delivery or a comminuted fracture of the head of the condyle. False ankylosis is produced by chronic disease of the soft tissues about the joint, causing a decrease in motion. However, there is nearly always some movement present. (Table 1.)

Limitation of jaw movement may arise from reflex irritation of the motor portion of the trigeminal nerve by inflammatory processes in the posterior portion of the floor of the mouth, and in the teeth and associated structures. This is called acute reflex trismus. Involuntary limitation may arise from disease of the lower third molar (pericoronar infection of a mandibular third molar), infection of the pterygomandibular space, fracture of the jaw at the angle of the mandible, periosteitis of the outer surface of the mandible, in-

jury to the masseter and pterygoid muscles, infection of the pharyngeal space, mumps, Ludwig's angina, and during dentition (the spasm will disappear in dentition when the erupting tooth pierces the mucous membrane).<sup>1-3</sup> Acute reflex trismus may occasionally persist for two weeks and is somewhat rare after exodontia.

Hysterical closure of the jaws occurs mainly in young females. The hysteria is diagnosed by the history and absence of a definitive lesion. The patient is usually of an unstable neurotic personality pattern; there is a history of many similar earlier attacks with sudden remissions. The onset of the attacks is usually associated with anxiety and mental strain, and the trismus may last for weeks. The amount of jaw movement varies and an absence of a physical cause for closure of the jaws may be shown by the production of relaxation by general anesthesia. (General anesthesia may also relax the trismus of tetanus but other physical facts are usually present to aid in the differential diagnosis [Table 1].) Psychotherapy by an experienced physician must be used as an active means of therapy for these patients.

Purely mechanical limitation of jaw movement may be due to inflammatory masses, neoplasms, or malunion of a fracture. In some cases of inflammatory disease limitation of the jaw movement may be voluntary due to pain.

The two most important muscles involved in trismus are the masseter and the internal pterygoid. The physician must differentiate between the inability to open the lips and the jaw. Inability to open the lips may be due to angioneurotic edema, and facial paralysis. When muscle spasm is present the spastic muscles may be felt to be hard and tense.

Tetanus is caused by infection with the virulent *Clostridium tetani*, a spore forming anaerobe. The incubation period is three days to several weeks. The shorter the incubation period the greater the mor-

TABLE 1  
*Differential Diagnosis of Trismus*

	TRUE ANKYLOSIS	FALSE ANKYLOSIS	HYSTERIA	STRYCHNINE	ACUTE REFLEX TRISMUS	TETANUS
Etiology	Extension of otitis media  Acute arthritis a. gonococcal b. metastatic septic c. tuberculosis (rare) d. traumatic	Progression of acute reflex trismus	Unstable emotional personality  Associated with nervous strain	Strychnine intoxication  No history of injury	Exodontia Infection 3rd mandibular molar Infection pterygomandibular space Fracture angle of jaw Mumps, Dentition	Cl. tetani History of wound
Clinical Picture	No jaw movement Also findings associated with spec. diseases Acute arthritis pain, tender swelling	Limited movement	No physical signs Movement under general anesthesia Usually in females May last weeks Amount motion varies	Jaw last to be affected Jaw drops after convulsion passes Tetanic cramps Rigidity	Only jaw involved, early	Gen. irritation Rigid neck and abdomen Convulsions Trismus Fever Increased CSF and spinal fluid pressure
Lab Findings	Leukocytosis X-ray*-obliteration of joint space	X-ray*-obliteration of joint space	None	None	None	Leukocytosis Culture Bacteriological examination of direct smear from wound
Therapy	Surgical intervention	Attempt to dilate May need surgical intervention	Psychotherapy	Emetics Sedation Curare Stimulants Supportive Artificial respiration	Soft diet Hot moist packs Supportive Reassurance not tetanus Oral care Penicillin for oral prophylaxis	TAT Sedation Curare Supportive Care wound

\* It is not easy to diagnose ankylosis by means of x-rays. In fibrous ankylosis the space between the condyle and the joint cavity is visible; in bony ankylosis it is absent. The lack of contrast between condyles and temporal bone produces unsatisfactory appearing x-rays, and many times it is impossible to determine whether the picture is poorly taken or lack of detail is due to the disease.<sup>10</sup>

tality. The disease may be divided into a prodromal and active phase. A patient in the prodromal phase exhibits generalized restlessness, hyperirritability, chilliness, headache, general stiffness of the body, and neck rigidity. Later, in the more active phase, there is trismus, board-like rigidity of the abdomen, fever of several degrees, leukocytosis, increased spinal fluid pressure, and severe pain due to muscle spasm. Consciousness usually persists until terminus. Death occurs commonly on the fourth to fifth day; the patient who survives until the eighth day in most cases recovers.<sup>4-6</sup>

Acute reflex trismus is characterized by spasm of

the masticating muscles of the jaw. The spasm is limited to the jaw area and there is no hyperirritability of any other muscles or groups of muscles. Occasionally there is an accompanying psychogenic retardation in deglutition with inability to swallow saliva. There is no generalized rigidity and the patient feels generally well. Fever and leukocytosis may result from the oral pathology initiating the reflex spasm.

The treatment of acute reflex trismus is:

1. Discover and treat the cause.
2. The application of continuous hot moist packs to the involved muscle area.
3. The maintenance of nutritional balance by a

high vitamin, high caloric, fluid diet. If the patient refuses to take food or is unable to do so because of the extreme trismus or difficulty with deglutition, intravenous alimentation must be resorted to as a method of therapy.<sup>1</sup>

Occasional complications of acute reflex trismus are fibrous changes in the muscles and soft tissues producing chronic false ankylosis. The contractures and false ankylosis are treated by gradual dilation of the jaw space, or if necessary, by surgical intervention.<sup>1</sup> It is felt that once the diagnosis of acute reflex trismus is made, consultation with a competent oral surgeon is mandatory.

The main therapy of tetanus is early diagnosis and the institution of intravenous, intraspinal, and intramuscular tetanus antitoxin, together with sedation by phenobarbital, rectal administration of paraldehyde, and general supportive measures. Beckman recommends 100,000 units of tetanus antitoxin in the first 24 hours in doses divided among intravenous (60,000 U divided in three doses), intraspinal (20,000 U), and intramuscular (20,000 U) administration. Injections of such strength may be continued for several days, later decreasing the dose to 10,000 to 20,000 U per day.<sup>7,8</sup> In spite of the urgency of therapy, the patient must be tested for sensitivity to the horse serum of the antitoxin before it is administered.

### CASE REPORT

Mrs. B. D., a 20-year-old white female had been complaining of a tooth ache and general oral distress on the lower right side of her mouth. There had also been occasional pain in the right ear. Dental examination revealed an impacted, decayed, and abscessed right lower third molar. X-ray examination confirmed the clinical diagnosis and the tooth was extracted under local anesthesia. The cavity (socket) left by extraction was packed with a sulfonamide preparation and the patient was placed on oral sulfadiazine medication.

The post exodontial period was uneventful until the third day when the patient noticed a slight stiffness of her jaws. This stiffness became more severe until the patient was unable to chew, and progressed to a marked limitation of jaw motion. Motion was finally (fifth day) completely lost and the patient was unable to separate her teeth. Speech was slurred, and the patient had much difficulty in taking nourishment and in controlling her saliva.

The patient and her family became markedly alarmed and called their physician. Physical examination revealed a distressed young woman who was

unable to open her jaws. Attempts to insert a tongue blade between the teeth were unsuccessful. The gums were dirty, there was fetor oris (the patient was unable to brush her teeth). There was enlargement of the right submaxillary lymph-nodes. The right ear drum was injected in the inferior portion. It was impossible to separate the teeth by gentle pressure. The masseter muscle on the right was hard and contracted. Temperature rectally was 100° F. The WBC was 11,500. No x-ray examination was possible as the patient refused hospitalization. General examination revealed no increased muscular irritability. A serious point arose for consideration when it was learned that the socket had been packed with a sulfonamide preparation, since reports have been published which indicate that tetanus organisms have been found to be present in unsterilized sulfonamide powder and ointment.<sup>9</sup> In view of the absence of specific signs of tetanus other than trismus and since it was known that an infected tooth had been extracted from the posterior portion of the right mandible, a diagnosis of acute reflex trismus was made. An effort was made to alleviate the patient and her family of any fear of lockjaw and its consequences. The patient was placed on a high caloric, high protein, high vitamin fluid diet, and continuous moist hot packs were applied to the right side of the face. Supplementary vitamins were administered parenterally.

Inasmuch as the patient was unable to carry out oral cleansing, and since the socket was exposed to the oral flora, particularly facultative pathogens, i.e., Vincent's organisms, 300,000 U of penicillin (Roman-sky formula) were given intramuscularly. It was explained to the patient that the active duration of the trismus could not be predicted and that watchful expectancy must be carried out. The patient was referred to an oral surgeon for continued management. The trismus showed signs of beginning remission by the ninth postoperative day; the patient opened her mouth 1/4 of an inch.

### COMMENT

It may be seen that reflex spasm of the masseter and pterygoid muscles after exodontia for an infected impacted lower molar may produce a clinical picture simulating lockjaw. Knowledge of the oral causes of trismus will prevent unnecessary physical and emotional hardship for the patient, the patient's family, and for the attending physician.

### SUMMARY

The causes, differential diagnosis, and therapy of acute reflex trismus after exodontia for an infected

tooth are discussed. A case report is presented. The need for rapid differential diagnosis is emphasized from the standpoint of good medicine, and for the physical and emotional well-being of the patient.

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### BIBLIOGRAPHY

1. Blair, V., and R. Ivy: *Essentials of Oral Surgery*, ed. 3, St. Louis, Mosby, 1944, pp. 380-403.
2. Mead, S.: *Oral Surgery*, ed. 3, St. Louis, Mosby, 1946, pp. 858-860, 860-872.
3. Prinz, H., and S. Greenbaum: *Diseases of the Mouth and Their Treatment*, Philadelphia, Lea & Febiger, 1935.
4. Christian, H.: *Osler's Principles and Practice of Medicine*, ed. 19, New York, Appleton-Century, 1942, pp. 200-206.
5. Yater, M.: *Symptom Diagnosis*, ed. 4, New York, Appleton-Century, 1942, pp. 234-235.
6. Pullen, R.: *Medical Diagnosis*, Philadelphia, Saunders, 1945, pp. 126, 145.
7. Beckman, H.: *Treatment in General Practice*, ed. 4, Philadelphia, Saunders, 1942, pp. 262-270.
8. Spaeth, R.: *Clinical study of tetanus*, *Am. J. Dis. Child.*, 60:130, 1940.
9. Fischer, C., et al.: *Bacterial contaminants in sulfanilamide ointment*, *J. A. M. A.*, 122:855-858, 1943.
10. Thoma, K.: *Clinical Pathology of the Jaws*, Springfield, Thomas, 1934, p. 150.

## BOOK REVIEWS . . .

**GYNECOLOGICAL AND OBSTETRICAL PATHOLOGY.** By Emil Novak, M.D. Second edition. 570 pages and 542 illus. Philadelphia, Saunders, 1947. \$7.50.

The second edition of Dr. Emil Novak's book on obstetrical and gynecological pathology is, like the first, an excellent standard reference work for the undergraduate student, resident and postgraduate student. The important clinical problems are thoroughly covered from the pathologic point of view and its aim is to be of assistance in the understanding of progress of the diseases discussed as well as in its diagnosis. It is profusely illustrated and has several colored plates which on the whole are good.

The chapters on carcinoma of the cervix, embryology, histology and ovarian tumors are outstanding, and the additions that have been made supplement the information contained in the original volume in a very practical and helpful way. The various diagnostic methods such as the Schiller test and Papanicolaou stain are discussed and properly evaluated.

The chapters on endometriosis and the relationship between hydatid mole and chorionepithelioma are very well handled.

The book should be in the library of every man who is doing or planning to do obstetrics and gynecology.

FREDERICK H. FALLS, M.D.

**THE WHY OF EXCESSIVE DRINKING AND THE HOW OF LICKING IT.** By Paul Fruhling. 20 pages. New York, William-Frederick Press, 1946. Paper 50¢.

This pamphlet offers a brief analysis of why a person becomes an alcoholic and how he may be treated. As a basis for the development of alcoholism he makes what he considers two basic statements: (1) "about 10 per cent of our population are emotionally or mentally unstable, or insane. (2) "over 60 per cent of our gainfully employed are doing work for which they have little or no natural aptitude, liking or interest and are vocational misfits."

Boredom leads to drinking, the author says, and 20 per cent of these drinkers will become alcoholics. He points out that an alcoholic is a sick person to whom alcohol is a necessity—a drug or an "anesthetic," no longer enjoyable as a stimulant or pleasantry.

From his experience in sanitarium treatment of alcoholics he discusses the breaking of the alcohol habit and the development of new habits in thinking and action and of a new philosophy relative to worry and personal troubles and a habit of relaxation. Lastly he points to the good works of the organization Alcoholics Anonymous.

R. H. K.

Answer to WHAT'S YOUR DIAGNOSIS?—Abscess of the liver due to streptococcus.

*Even with the advent of the newer chemotherapeutic agents and antibiotics, meningitis remains a serious disease and it is relatively frequent. Early treatment is very important and that means early diagnosis. Both are discussed in this paper.*

## The Common Meningitides: Diagnosis and Treatment\*

LEWIS K. SWEET, M.D.

WASHINGTON, D. C.

Modern advances in the precision treatment of the various types of pyogenic meningitis have reduced the mortality from this group of diseases by very substantial margins. The intelligent application of the various antibiotic and chemotherapeutic agents, however, requires that exact etiologic diagnoses be made very promptly after meningitis is suspected. The purpose of the present paper is to outline the procedures for diagnosing and treating meningitis now in use in the Gallinger Municipal Hospital, and to discuss briefly the results that have been obtained by these methods.

### DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS OF MENINGITIS

Of utmost importance in making a diagnosis of meningitis is the knowledge of when to suspect the disease. In the average patient with a rather acute history of fever, headache, and vomiting, with or without a skin rash, but with nuchal rigidity and a positive Kernig or Brudzinski sign, the diagnosis is readily suspected and can be confirmed immediately by lumbar puncture. It is at the extremes of life when difficulty in suspecting meningitis is encountered. In infants there may be few or none of the classical signs.<sup>1</sup> The infant may be ill, without evident localization. The fontanelle usually is full, but even this sign is absent at times. Recently we had one infant with pneumonia who continued to run a fever and to appear ill in spite of adequate chemotherapy. The fontanelle was soft, the neck flexible, and there were no other signs of meningitis. Lumbar puncture, however, yielded a grossly purulent fluid that contained numerous *H. influenzae*. Accordingly it is our practice to suspect meningitis in any infant who is ill without evident cause. Likewise any infant or young child who suffers repeated convulsions must be suspected of meningitis.

The diagnosis of meningitis is often obscure in elderly patients also. The older the patient, the more

difficult the diagnosis. In our experience, the two conditions that most frequently obscure the diagnosis of meningitis are acute alcoholism and a cerebrovascular accident. It is our policy to appraise carefully all such patients and, unless meningitis can be excluded, to perform a lumbar puncture. Likewise, the study of any patient who is in a coma or who is completely disoriented and delirious must include a lumbar puncture unless another diagnosis can be made positively and immediately.

The question of the advisability of a lumbar puncture in the presence of evident bacteremia is raised frequently. Recently Pray<sup>2</sup> has shown that there is no practical reason to avoid lumbar puncture in the presence of a pneumococcal bacteremia. Likewise, the experience in this hospital with acute meningococcemia bespeaks the innocuousness of this procedure.<sup>3</sup> We have had 12 patients with meningococcemia on whom lumbar puncture was done within an hour or two of the times the blood that contained meningococci was withdrawn for culture. In no instances did meningitis supervene, nor have we had any patient with meningococcal meningitis whose initial spinal fluid failed to show meningococci on smear or culture.

The immediate etiologic diagnosis of meningitis must rest upon the examination of the spinal fluid. There are no uniform or characteristic findings from either the history or the physical examination upon which an absolutely reliable diagnosis can be based, though the presence of a characteristic rash<sup>3,4</sup> is strongly suggestive of a meningococcal infection. The studies by which a diagnosis can be made are as follows:

I. Culture. It is our practice to inoculate two chocolate agar slants directly from the spinal needle. By this method a high percentage of positive results are obtained, and the results of the immediate studies are confirmed.

II. Cell count. Both total cells and leukocytes

\* From the Infectious Disease Service, Gallinger Municipal Hospital, and the Department of Pediatrics, George Washington University School of Medicine.

must be counted. If the ratio of leukocytes to erythrocytes is greater than that found in the circulating blood, meningitis must be considered to be present in the presence of hemorrhage. This circumstance occurs not infrequently.

If erythrocytes are present, the presence or absence of crenation must be noted immediately.

### III. Centrifugation and examination of sediment.

A. The appearance of the supernatant fluid should be recorded.

B. A rather thick film of the sediment should be examined by:

1. Methylene blue stain for a differential count of leukocytes and for the number and shape of organisms. Bacteria are seen much more frequently when stained by the methylene blue than by most other stains.

2. Gram stain for the staining reaction of organisms.

C. On the supernatant fluid the following should be obtained:

1. Guaiac test if the original fluid was bloody.

2. Protein content. It is our practice to obtain the total protein as being much more reliable than the tests for globulin.

3. Dextrose. A satisfactory immediate determination is the five tube method outlined by Alexander and her associates<sup>5</sup> in which 1.0 cc. of Benedict's qualitative solution and progressive amounts of from 0.05 to 0.25 cc. of spinal fluid, by increments of 0.05 cc., are placed in the tubes before boiling. If there is reduction of the Benedict's solution by 0.10 to 0.15 cc. of spinal fluid, the dextrose is within the normal range. If there is no reduction with 0.25 cc., the dextrose is less than 10 mg. per cent.

There are three pathologic processes that commonly cause meningeal irritation. These, together with the characteristic spinal fluid findings are outlined in Table 1. It is of great importance to note that, early in meningitis especially, bacteria may be in the spinal fluid without there being any other abnormal findings. Therefore, even when a clear fluid is obtained, organisms must be sought for by smear and by culture. The diagnosis of meningitis must be entertained in acutely ill patients until the cultures fail to reveal organisms.

It is our custom, in determining the etiologic diag-

TABLE 1  
*Causes of Meningeal Irritation*

LESION	CHARACTER OF SPINAL FLUID
Toxemia (Meningism)	Increased pressure. Otherwise normal.
Trauma (Subarachnoid hemorrhage)	Uniformly bloody fluid. Red blood cells usually are crenated. Supernatant fluid usually is xanthochromic. Guaiac test on supernatant fluid may be positive.
Inflammation (Meningitis)	Leukocytes increased or bacteria present.

nosis in a given patient with meningitis, to differentiate as to whether we are dealing with a serous or a purulent meningitis. This is done (Table 2) by de-

TABLE 2  
*Characteristics of the Cerebrospinal Fluid in Serous and Purulent Meningitis*

CHARACTERISTICS OF SPINAL FLUID	SEROUS	PURULENT
Total cells	10 to 3,000	Normal to 250,000
Predominant type of cells	Mononuclear	Polymorphonuclear
Dextrose	Normal or decreased	Decreased or normal
Protein	Increased	Increased
Culture	Sterile	Bacteria or sterile

termining the predominant type of cell in the spinal fluid. Occasionally the differential cell count will change significantly, but as a rule even in such conditions as poliomyelitis the ultimate cytology will be reflected in the initial spinal fluid.

Acute serous meningitis may be caused by many etiologic agents (Table 3). In only rare instances can an exact diagnosis be made immediately and with certainty. The absence, or a marked reduction, of the spinal fluid dextrose is very suggestive of a bacterial (tuberculous) infection, though any patient with extensive vomiting and a prolonged fast may show considerable reduction of dextrose. Acid-fast bacilli may best be demonstrated by the method of Hanks and Feldman.<sup>6</sup> Syphilitic meningitis can be diagnosed by the serologic reactions, and/or a positive darkfield in some instances. Leptospiral meningitis and the various primary virus infections must be diagnosed by the demonstration of the infecting agent in the body fluids, or by the development of antibodies in the blood during convalescence.

One recently encountered type of acute serous meningitis,<sup>7-9</sup> that associated with scarlet fever, deserves a

TABLE 3  
*Differentiation of Serous Meningitis*

TYPE	CHARACTER OF SPINAL FLUID			
	Cells	Protein	Dextrose	Other
<b>Virus</b>				
1. Primary Infection				
A. Lymphocytic choriomeningitis	90% or more lymphocytes	Increased	Normal	Virus may be in spinal fluid
B. Poliomyelitis	Variable	Increased	Normal	Paralysis may be associated
C. Encephalitis (various forms)	Variable	Increased	Normal	
2. Secondary Infection (following rubeola, epidemic parotitis, varicella and rubella)	Variable	Increased	Normal	
3. Rare and at present unknown virus infections.	Variable	Increased	Normal	
<b>Bacterial-Tuberculosis</b>	70% lymphocytes	Markedly increased	Reduced	Acid-fast bacilli in spinal fluid
<b>Spirochetal</b>				
1. Syphilis	Variable	Increased	Normal	Serology positive
2. Weil's disease	70-90% or more lymphocytes	Increased	Normal	Usually have associated icterus, positive agglutination
<b>Irritative—Chronic inflammation impinging on the meninges</b>	Variable	Increased	Normal	
<b>Chemical—Lead poisoning</b>	Variable	Increased	Normal	Chiefly in children. Lead line in x-ray of bones
<b>Fungus—Torula</b>	Variable	Normal	Normal	Torula on smear and culture
<b>Protozoa—Toxoplasmosis</b>	Variable	Normal	Normal	Areas of calcification in the brain
<b>Unknown—Serous meningitis in scarlet fever</b>	90% or more lymphocytes	Increased	Normal	Following scarlet fever in children

special comment. The essential features of the eleven patients previously described by us<sup>9</sup> are summarized in Tables 4, 5, and 6. Figure 1 shows a typical tem-

TABLE 4  
*Clinical Features of Eleven Cases of Acute Serous Meningitis Complicating Scarlet Fever*

FEATURE	LOW	HIGH	MEDIAN
Age	3	9	7
Onset—days after onset of scarlet fever	5	8	6
Temperature (degrees Fahrenheit)	102	105	104
Duration of fever (days)	5	9	6
Duration of pleocytosis spinalis (days)	6	26	12

perature curve. There were no race, sex, or seasonal predilections other than those encountered with scarlet fever. The complication occurred only in children and was seen more frequently after moderately toxic or toxic scarlet fever, four and six cases respectively, than after a mild attack, one case. The treatment of the original scarlet fever had no bearing on the incidence of the complication. In almost all these patients the signs of meningeal irritation were minimal and had to be sought for with care. Lasson and Bang<sup>7</sup> report the finding of cerebrospinal fluid changes in scarlet fever patients who suffer a recur-

TABLE 5  
*Cerebrospinal Fluid Findings in Eleven Cases of Acute Serous Meningitis Complicating Scarlet Fever*

TEST	LOW	HIGH	MEDIAN
Total cells	32	1100	174
Percentage of lymphocytes	75	100	95
Dextrose	43	76	70
Total protein	25	100	65
Chlorides	610	693	660

TABLE 6  
*Blood Findings in Eleven Cases of Acute Serous Meningitis Complicating Scarlet Fever*

	LOW	HIGH	MEDIAN
Total leukocytes ( $\times 1,000$ )	11.8	32.0	20.0
Polymorphonuclear neutrophils (%)	63	86	75
Young polymorphonuclear neutrophils (%)	11	34	20

rent fever without evidences of meningeal irritation. At present, it seems wise to do lumbar punctures on all scarlet fever patients with an unexplained secondary rise in temperature during the first two weeks of the disease.

The etiology of this disease (or complication) is as yet unknown. The clinical picture strongly suggests a virus infection in all respects except the leukocyte





FIG. 1. Acute serous meningitis in scarlet fever. Patient entered the hospital on third day of illness with moderately severe scarlet fever. Treated with antitoxin and sulfanilamide. Slight meningeal irritation on October 3rd. Spinal fluid contained 180 cells per mm., 94 per cent lymphocytes; protein 100 and dextrose 58 mg. per cent. Blood showed 25,650 leukocytes with 65 per cent neutrophils (15 per cent immature forms). Treatment was symptomatic. Recovery was complete.

count, but no virus has yet been isolated from the patients.<sup>9</sup> Recovery has been prompt and without evident sequelae in all the patients we have studied.

The etiologic diagnosis of purulent meningitis is much more successful than is the case with serous meningitis and can be made immediately (within an hour or two) with a high degree of accuracy in 80 per cent or more of all cases studied. The common bacteriologic findings as encountered on the original direct smear of the spinal fluid sediment are outlined in Table 7. Whenever gram-negative intra- and extracellular diplococci are seen in reasonable numbers (2 or 3 or more per field) direct Neufeld typing with anti-meningococcic group I and group II alpha serum should be attempted. If there is definite capsule swelling (usually less marked than with the pneumococcus or *H. influenzae*) the diagnosis is certain. Group II meningococcus can be proved only by agglutination of the culture. Differentiation of the gonococcus from the meningococcus requires more precise bacteriology. Clinically, however, the differentiation is of no importance as the two organisms respond equally well to the sulfonamides or penicillin.

All gram-positive cocci should be subjected to immediate Neufeld typing against the various antipneumococcic sera, and all gram-negative bacilli should be similarly typed against *H. influenzae* type b serum. If these typings are not successful, exact diagnosis must await the results of culture. However, the morphology and staining characteristics of the bacteria offer important clues to the diagnosis, and appropriate treatment may be instituted at once.

If there are no demonstrable organisms on the direct smear, the presence or absence of dextrose in the spinal fluid is of great importance to diagnosis. If

TABLE 7

### Differentiation of Purulent Meningitis

- I. Organisms visible on direct smear. Dextrose always low.
  - A. Meningitis due to cocci
    1. Gram-negative cocci
      - (a) Meningococcus—Intra- and extracellular biscuit-shaped diplococci. If numerous, groups I and IIa can be typed by Neufeld technic.
      - (b) Gonococcus—Identical with meningococcus in smear. Not typable. Rarely invade the meninges.
    2. Gram-positive cocci
      - (a) Pneumococcus—Lancet-shaped diplococci. Neufeld typing done directly on spinal fluid.
      - (b) Streptococcus—Cocci in pairs and chains. Do not type with pneumococcus sera.
      - (c) Staphylococci—Cocci in pairs and clusters. Do not type with pneumococcus sera.
  - B. Meningitis due to bacilli—All gram negative.
    1. Hemophilus influenzae.—Very pleomorphic rods. Type with specific serum by Neufeld technic. Precipitin test positive.
    2. Organisms of the colon-typhoid group—Not pleomorphic, and not typable with *H. influenzae* serum.
  - C. Other organisms—Very rarely any other organisms, either pathogenic or nonpathogenic may cause meningitis and be present in the spinal fluid.
- II. Organisms not demonstrable on direct smear.
  - A. Spinal fluid dextrose is reduced; is bacterial meningitis. May be due to any organism, but more frequently is due to the meningococcus.
  - B. Spinal fluid dextrose is normal.
    1. Bacterial meningitis (early). Confirm by culture.
    2. Meningitis from an acute purulent focus impinging on the meninges.
      - (a) Brain abscess, or multiple embolic abscesses from bacterial endocarditis.
      - (b) Mastoid abscess.

the dextrose is greatly reduced or absent, it is almost certain that there is direct bacterial invasion of the meninges. This finding may occur with any infecting organism, and the results of culture alone can establish the diagnosis. However, as will be shown below, the absence of organisms in the original spinal fluid is of good prognostic significance and unusual or heroic therapeutic procedures usually are not indicated in these patients. If, on the other hand, the spinal fluid dextrose is normal the presumption is strong that the meningitis, if of bacterial origin, is in an early stage. However, it may mean that the meningeal reaction is secondary to an infectious process impinging on the meninges, and that direct bacterial invasion of the meninges has not taken place. This occurs more frequently at present with brain abscess, either solitary or multiple (from emboli thrown off in bacterial endocarditis) though formerly it was a frequent complication of acute mastoiditis with epidural abscess formation.

## TREATMENT OF MENINGITIS

There are certain basic principles in the care of patients with meningitis that must apply to all patients regardless of the type of infection with which they suffer. These include:

1. Bed rest.
2. Good nursing and general supportive care.
3. Adequate fluids and electrolytes. Many patients with meningitis may have vomited considerably, and will have undergone a period of more or less starvation before the physician sees them. Therefore, almost all patients will be dehydrated, many severely so. It is of utmost importance to correct this dehydration with fluids and electrolytes (isotonic salt solution, Ringer's solution, dextrose, etc.) as rapidly as possible. If sulfonamides are to be given parenterally the dehydration must be corrected before or with the administration of the sulfonamide compound.

4. Sedation. Meningitis patients almost as a rule have a severe and excruciating headache that often causes extreme restlessness. This pain can, in my opinion, be controlled best by morphine. While morphine causes respiratory depression and increase of intracranial pressure, these disadvantages are much more than offset by sedative action of the drug. The use of other sedatives, with the possible exception of demerol, is almost useless because of their impotence.

5. Care of the bladder and bowels. There often is transitory urinary retention in meningitis, and the presence of a large, distended bladder contributes materially to the restlessness and discomfort of the patient. Catheterization is essential in this situation and may reduce the need for sedation.

In addition to the above regime, which must apply alike to all patients with serous or purulent meningitis, all patients with purulent meningitis, with the possible exception of those with *H. influenzae* infection, should receive one of the sulfonamide compounds. We have used sulfadiazine or sulfamerazine with equal results.<sup>10</sup> Recently a combination of sulfadiazine and sulfamerazine has been used, the results of which are soon to be reported.<sup>11</sup> The dosage that we have employed of sulfadiazine or sulfamerazine has been 6.0 Gm. immediately and 1.0 Gm. every four hours for adults. For children we have used 70 mg. per kilo ( $\frac{1}{2}$  gr. per pound) immediately and 150 mg. per kilo (1 gr. per pound) per day, divided into six equal doses and given every four hours. If the patient is unable to swallow, or is vomiting excessively, the initial dose may be given intravenously in 0.5 per cent concentration in isotonic salt solution. More concentrated solutions greatly enhance the danger of

renal calculus formation and should not be used initially. Succeeding doses may be given intravenously or subcutaneously in 0.5 to 5.0 per cent solution (depending upon the state of hydration of the patient), or may be given through a stomach tube if the patient is not vomiting excessively. The latter route gives more stable blood concentrations than do parenteral injections. Oral administration of the sulfonamides is preferable, of course, if the patient can take and retain the drug. This route is quite satisfactory for even the initial dose in those patients who are able to co-operate.

**Meningococcic Meningitis.** In meningococcic meningitis the chief adjunct to the basic therapy outlined above, is penicillin. This agent has now replaced completely the serum that was used in severely ill or unfavorable patients in former years. Penicillin is used immediately in the comatose or irrational patient, especially when he is over 40 years of age, in the patient with fulminating meningococcic infections, and in any patient whose response after 24 to 48 hours of sulfonamide and general treatment has been unsatisfactory. The dose that we employ is 20,000 units intrathecally every 12 hours for three doses and once per day thereafter. With this is combined the intramuscular injection of amounts ranging from 200,000 to 500,000 units for most patients. The intramuscular penicillin may be increased to 2,000,000 units daily in fulminating infections or more severely ill patients. This preferably is given by continuous intramuscular drip, but may be given in 12 equal doses at two-hour intervals if the patient cannot tolerate the drip.

The results obtained with this type of treatment in 207 previously reported patients<sup>12</sup> are summarized in Tables 8, 9, and 10. The factors of greatest importance in making a prognosis on patients with meningococcic meningitis are the age of the patient, the condition of the sensorium at the time treatment is started and, if the patient is comatose or irrational, the number of organisms and the extent of the reduction of dextrose in the original spinal fluid. As is shown in Table 8, the older the patient, the less favorable the

TABLE 8

*The Outcome of Meningococcus Meningitis in Relation to the Age of the Patient*

AGE	TREATED	DIED	
	Number	Number	Per Cent
Total	207	21	10.1
0-9	31	0	0.0
10-39	126	9	7.1
40-70	50	12	24.0

outlook. Very young infants also have a more serious prognosis, a fact not shown in the table.

The factor of the greatest prognostic significance, however, is the state of the patient's sensorium at the time treatment is started (Table 9). Among 113 pa-

TABLE 9

*Outcome of Meningococcic Meningitis in Relation to the Patient's Sensorium at the Time of Treatment, and to the Age in Comatose or Delirious Patients*

SENSORIUM	TREATED	DIED	
	Number	Number	Per Cent
Total	207	21	10.1
Rational on admission	113	1	0.9
Comatose or delirious on admission			
0-9 years	5	0	0
10-39 years	55	8	14.5
40-70 years	34	12	35.3
Subtotal	94	20	21.3

tients who were rational on admission, there was only one death, that in a young girl with an extraordinarily severe, fulminating infection. However, among 94 patients who were completely disoriented or who were in a coma, there were 20 deaths. Likewise, the older the patient in the coma-delirium state, the more grave the prognosis. And finally (Table 10) among those

TABLE 10

*Outcome of Comatose or Delirious Patients with Meningococcus Meningitis in Relation to the Number of Organisms and the Dextrose Content of the Original Spinal Fluid*

SPINAL FLUID FINDINGS	TREATED	DIED	
	Number	Number	Per Cent
Total	94	20	10.1
Many organisms*—Dextrose less than 10 mg. per cent	28	7	25.0
Many organisms*—Dextrose more than 10 mg. per cent	15	4	26.7
Few or no organisms—Dextrose less than 10 mg. per cent	24	6	25.0
Few or no organisms—Dextrose more than 10 mg. per cent	27	3	11.1

\* Many organisms—4 or 5 or more per oil immersion field in a centrifuged sediment.

patients who are in a coma or a delirium when treatment is started, the presence of many organisms (4 or 5 or more per oil immersion field in a centrifuged sediment) or the virtual absence of dextrose in the original spinal fluid specimen is of more serious prognostic significance.

**Pneumococcic Meningitis.** All patients with this type of meningitis should have, in addition to the basic regime of treatment outlined above, immediate

treatment with penicillin. This is given intrathecally in dosages of 20,000 units in 20 cc. of distilled water or isotonic salt solution every 12 hours for three doses, then once daily. In extremely severe illnesses, the dose may be increased to 40,000 to 50,000 units in the same volume of diluent for a few doses. It is our opinion, however, that the prolonged administration of intrathecal penicillin in concentrations greater than 1,000 units per cubic centimeter may have been the precipitating factor in causing the nervous complications of intrathecal penicillin administration previously reported from this clinic.<sup>13</sup> It is possibly significant that the only complication of this type that we have encountered since we have adhered strictly to a concentration of 1,000 units per cubic centimeter for intrathecal use was in a man to whom, through error, 200,000 units in 20 cc. of diluent was given in a single injection.

Intramuscular penicillin is given to patients with pneumococcic meningitis in this hospital in amounts ranging from 500,000 to 1,000,000 units daily, with some patients being given two or even five million units per day by this route. This is given by continuous intravenous drip, or by frequently repeated injections. We have discontinued the use of antipneumococcic serum in these patients.

The factors of prognostic significance in pneumococcic meningitis are much the same as those for meningococcic meningitis, with the addition that the primary focus of disease leading to the meningitis is also of utmost importance. Tables 11 through 14 show the outcome of 53 patients with pneumococcic meningitis treated as outlined above, in relation to the various prognostic standards. The number of patients under 40 years of age that we have treated is small (Table 11), but there is a sharp increase in mor-

TABLE 11

*The Outcome of Pneumococcic Meningitis in Relation to the Age of the Patient*

AGE	NUMBER TREATED	NUMBER DIED
Total	53	31
0-9	5	2
10-39	8	2
40 and over	40	27

talidity at 40 years. Above the age of 40 years, there is little variation in mortality until the age of 60 has been passed, at which time the prognosis again worsens decidedly.

The primary focus of disease leading to a pneumococcic meningitis is of the greatest prognostic significance (Table 12). Those patients whose infection arises from an otitis media or mastoiditis, and those

TABLE 12

*Outcome of Pneumococcic Meningitis in Relation to the Primary Pneumococcic Infection*

PRIMARY FOCUS	TREATED	DIED
Total	53	31
Pneumonia	19	13
Otitis and/or mastoiditis	10	2
Endocarditis	2	2
Head injury	1	0
Unknown	11	11
None (primary meningitis)	10	3

in whom the disease apparently is primary and without antecedent focus offer the best outlook, while those patients who are too ill to permit a clinical recognition of the primary focus before death, and those patients whose primary focus is endocarditis or pneumonia fare much less well. It is in these latter patients that massive doses of penicillin must be employed.

As is the case in meningococcic meningitis, the sensorium of the patient when treatment of pneumococcic meningitis is instituted is of considerable significance (Table 13). Patients who are in a coma have

TABLE 13

*Outcome of Pneumococcic Meningitis in Relation to the Patient's Sensorium at the Time of Treatment*

SENSORIUM	NUMBER TREATED	NUMBER DIED
Total	53	31
Rational	9	4
Irrational	12	2
Comatose	25	19
Not recorded	7	6

an extremely bad prognosis, while those who are rational fare much better. The excellent results among patients who are irrational but not comatose is not explained. The number of organisms in the original spinal fluid specimen (Table 14) is also of definite

TABLE 14

*Outcome of Pneumococcic Meningitis in Relation to the Number of Organisms in the Original Spinal Fluid*

NUMBER OF ORGANISMS IN ORIGINAL SPINAL FLUID	NUMBER TREATED	NUMBER DIED
Total	53	31
Sufficient for immediate typing	35	24
Too few for typing	17	6
Not recorded	1	1

prognostic significance. If the fluid is teeming with organisms, the outlook is almost hopeless, while if there are few or no organisms demonstrable directly, the prognosis is greatly enhanced. In fact, if the etio-

logic diagnosis must await the results of spinal fluid culture, it is not uncommon for the patient to show so much clinical improvement as to render the administration of penicillin unnecessary.

**Hemophilus Influenzae Meningitis.** The treatment of choice in this disease has been, until recently, that outlined by Alexander and her associates<sup>5, 14, 15</sup> whereby highly potent rabbit antiserum was combined with sulfadiazine and good general care. The recent introduction of streptomycin to which the bacillus has proved to be susceptible, has altered the approach to this disease, however. Good results with streptomycin alone have been reported by Alexander,<sup>16</sup> Weinstein<sup>17</sup> and others. The exact dosage of streptomycin has not been established. Alexander recommends 20 mg. per pound body weight per day intramuscularly, and 25 to 50 mg. intrathecally once a day for five days. Weinstein has used an average of 1.0 Gm. per day by intramuscular injection (regardless of the size of the child) and from 10 to 25 mg. intrathecally every day. He continued his intramuscular injections for from seven to nineteen days, and intrathecal injections for from four to seven days longer, usually for not less than two weeks.

Our experience with streptomycin in *H. influenzae* meningitis has been too limited for an appraisal to be made. However, it seems reasonable at present to treat patients with this disease with streptomycin both intramuscularly (the dose may have to be raised 2 or even 4 Gm. per day) and intrathecally (25 to 50 mg. per day). The treatment should be continued at least until cultures are negative and the patient has been afebrile for from three to five days. If the patient does not respond favorably within 24 or 48 hours, *H. influenzae* rabbit antiserum probably should be given in doses of 100 to 200 mg. of antibody nitrogen (4 to 8 vials) intravenously. If facilities are available to check the patient's blood serum for antibody content<sup>14</sup> this should be done, and a titer of 1:8 or more of antibody should be maintained in the serum. If this test is not available, the initial dose of serum should be at least 200 mg. of antibody nitrogen. Patients who are comatose or who are under six or seven months of age may require the combined administration of streptomycin, serum and sulfonamides from the inception of treatment.

## SUMMARY

The differential diagnosis of meningitis has been discussed. At present it usually is very difficult to arrive at an etiologic diagnosis promptly in patients with an acute serous meningitis. However, in pa-

tients with an acute purulent meningitis an exact etiologic diagnosis can be made with a high degree of success by careful cytologic, chemical, and bacteriologic examinations made in an ordinary clinical laboratory within an hour or two after the patient is seen. The procedure for making such a diagnosis is outlined.

There are certain basic principles to be applied in the treatment of all forms of meningitis. All such patients should be given bed rest, good nursing care, adequate fluids and electrolytes, and adequate sedation. All patients with purulent meningitis, with the possible exception of those with *H. influenzae* infections, should receive one of the sulfonamide compounds (sulfadiazine or sulfamerazine) also. Meningococcic meningitis usually will respond to the basic regime outlined, though certain patients will require the use of penicillin. Penicillin should be given in large doses to all patients with pneumococcic meningitis. Streptomycin offers promise of being the drug of choice in treating meningitis due to the *Hemophilus influenzae*, though the co-ordinate status of the sulfonamide compounds and of antiserum remains to be established.

### BIBLIOGRAPHY

1. McKhann, Charles F.: Meningococcus meningitis in infants, *New England J. M.*, 202:520, 1930.
2. Pray, L. G.: Lumbar puncture as a factor in the pathogenesis of meningitis, *Am. J. Dis. Child.*, 62:295, 1941.
3. Sweet, L. K., Harry F. Dowling, and M. Jane Howell: Acute meningococcemia, *J. Pediat.*, 30:438, 1947.
4. Daniels, Worth B., S. Solomon, and William A. Jaquette: Meningococcic infection in soldiers, *J. A. M. A.*, 123:1, 1943.
5. Alexander, Hattie E., C. Ellis, and G. Leidy: Treatment of type-specific *Hemophilus influenzae* infections in infancy and childhood, *J. Pediat.*, 20:673, 1942.
6. Hanks, John H., and Harry A. Feldman: The concentration of tubercle bacilli from spinal fluid by means of chemical flocculation and lipid solvents, *J. Lab. & Clin. Med.*, 25:886, 1940.
7. Lasson, H. C. A., and J. Bang: Aseptic complications from the central nervous system through scarlet fever, *Nord. Med.*, 8:2130, 1940.
8. Nielsen, G.: Serous meningitis as a complication of scarlet fever, *Ugesk. F. Laeger.*, 103:942, 1941.
9. Sweet, L. K., and Mark H. Lepper: Acute serous meningitis in scarlet fever, *J. Pediat.*, 24:295, 1944.
10. Lepper, M. H., L. K. Sweet, and H. F. Dowling: The treatment of meningococcic infections with sulfadiazine and sulfamerazine, *J. A. M. A.*, 123:134, 1943.
11. Zeller, W. W., H. L. Hirsh, L. K. Sweet, and H. F. Dowling: The treatment of meningococcic, pneumococcic and other types of meningitis with sulfadiazine and sulfamerazine combined, *J. A. M. A.* (In press).
12. Sweet, L. K., E. Dumoff-Stanley, and H. F. Dowling: Meningococcic meningitis treated with sulfadiazine and sulfamerazine. A three year study, *Ann. Int. Med.*, 23:338, 1945.
13. Sweet, L. K., E. Dumoff-Stanley, H. F. Dowling, and M. H. Lepper: The treatment of pneumococcic meningitis with penicillin, *J. A. M. A.*, 127:263, 1945.
14. Alexander, H. E.: Experimental basis for treatment of *Hemophilus influenzae* infections, *Am. J. Dis. Child.*, 66:160, 1943.
15. Alexander, H. E.: Treatment of *Hemophilus influenzae* infections and of meningococcic and pneumococcic meningitis, *Am. J. Dis. Child.*, 66:172, 1943.
16. Alexander, H. E.: Streptomycin in pediatrics, *J. Pediat.*, 29:192, 1946.
17. Weinstein, Louis: The treatment of meningitis due to *Hemophilus influenzae* with streptomycin, *New England J. M.*, 235:101, 1946.

### Study Material Available

The Army Institute of Pathology in Washington, D. C., has arranged to loan Veterans Administration hospitals and homes study and review material containing the latest available information on the causes and development of diseases.

The materials will be used by VA in clinicopathologic conferences, medical meetings and training programs, as part of an over-all VA program of training medical personnel.

The Institute has agreed to supply sets of study material without the usual deposits and rental fees, provided they are used in recognized training programs, operated on definite schedules.

Available material includes study sets of histo-

pathologic slides (pertaining to diseases of the tissue), clinical abstracts, lantern slides, atlases and syllabuses.

The slide sets cover a variety of diseases, such as endocrine, breast and bone tumors, kidney and fungus diseases, skin disorders, thyroid-gland pathology and tropical diseases.

The atlases and syllabuses include dental and oral pathology, genito-urinary pathology, kidney diseases, fungus diseases, and others.

The VA directive, describing this service, suggested to hospital managers that "a more comprehensive and instructive teaching and training program will be achieved if field stations utilize this material placed at their disposal by the Army Institute of Pathology."

*Worm infection is more frequent than is generally recognized. The following two papers review the subject and outline the most acceptable methods of treatment.*

## Pinworm Infection and Trichinosis\*

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During the last several years, a great amount has been written regarding the importation of parasitic diseases from outside the United States. Filariasis and schistosomiasis were acquired by considerable numbers of troops and, from a military standpoint, were the most important of these exotic helminthic diseases. The evidence accumulated to date indicates that neither of these diseases will become established in this country due, in part, to the spontaneous recoveries from filariasis and to the institution of prompt and adequate therapy of schistosomiasis.

In the last decade, new knowledge has accumulated regarding some of our indigenous helminthic diseases and a review of these diseases appears timely. This and the succeeding paper deal with the worm diseases commonly seen in medical practice.

### PINWORM INFECTION

Pinworm infection is considered first because this is our commonest worm parasite in the United States and because our greatest strides in the knowledge of this infection were made in recent years. Cram<sup>1</sup> in 1943 reviewed the studies made by the National Institute of Health on this subject.

One of the most startling observations that has been made is the high incidence of the infection. For example, examinations made upon certain school children from Washington, D. C. upon arrival at a summer camp indicated that 57 per cent were infected. That this was not an isolated instance of a high infection rate has been proved by many random surveys in various localities.

Certain generalities may be given with regard to the incidence of the disease. The infection may be acquired during infancy but ordinarily the highest incidence occurs during the school years. The incidence declines in adolescents due to spontaneous recoveries. The infection is often acquired again in adult life when children reintroduce the parasite into

the household. The pinworm is more common in whites than Negroes. It is also more common in temperate than in tropical climates.

The parasitism often involves all members of a household; the introduction of the parasites by one member predisposes all others to the infection. The more lightly infected cases show evidence of infection intermittently but since the worms probably require about four weeks to mature, such cases may be considered as harboring developing parasites at nearly all times in spite of negative examinations.



FIG. 1. A female pinworm migrating in the anal folds. Magnified about six times.

The mature female pinworm migrates out of the anus during periods of host inactivity (Fig. 1), deposits about 10,000 eggs, and then dies. The male dies within the intestine and passes out with the feces al-

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Presented before the American College of Internal Medicine, D. C., on October 22, 1946.



FIG 2. Mature female pinworms The dark part of the worm in this picture consists almost entirely of eggs  
Magnified 15 times

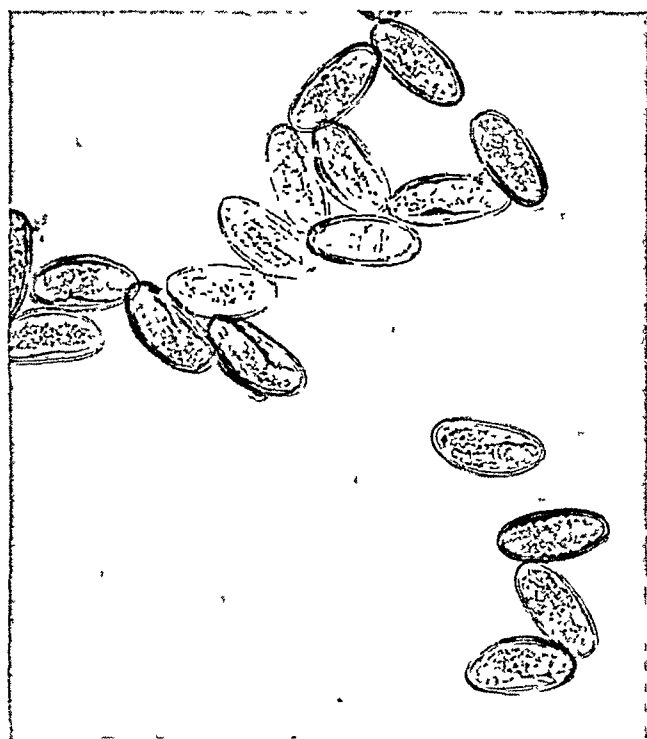


FIG 3. Pinworm ova. Magnified 260 times.

though we have sometimes recovered males from the perianal region. The eggs are not infectious when first deposited but mature in about six hours. The eggs are not only spread through hand to mouth transmission but are light enough to be borne about the household by air currents. Thus in infected homes, they have been found on the lintels and chandeliers. By one means or another, eggs get into the mouth and the larvae develop in the intestine. There is no reproduction within the host; an egg must have been swallowed for every worm produced. None of the

lower animals is known to harbor the human pinworm and only man can be incriminated as a reservoir host.

The degree of infection varies greatly. We have removed, by count, 5,000 pinworms from a single case. We have seen as many as 13 matured female worms migrating on the perianal region at one time. The majority of cases, however, average less than one migrating worm nightly.

Cases are usually referred to the physician because of anal itching or because the observant mother has seen migrating pinworms. The female is white and about one-half an inch in length when mature. When migrating, she is active but when brought to the physician, she is usually dried out and shrivelled. The ova are expelled in festoons by peristaltic uterine contractions when the worm is dying. Figure 2 shows the mature female pinworm. The eggs are readily identified by their jelly-bean shape with one flattened side (Fig. 3).

The degree of discomfort caused by the migrating parasites is variable. Many infected persons deny any sensation due to the migrating worms, this is particularly true of children. Some children and most adults complain of a mild tickling sensation in the lower rectum if a migration occurs when awake. In a few persons, the worms upon migration cause an almost intolerable itching with consequent restlessness, scratching, and insomnia. Symptoms due to the presence of developing worms within the intestine are more difficult to evaluate. Abdominal pain has been attributed to the infection. In one case in our series, periodic nausea and vomiting before breakfast seemed to be related to the infection.

The role of the pinworm in producing appendicitis is debatable. The finding of pinworms within the

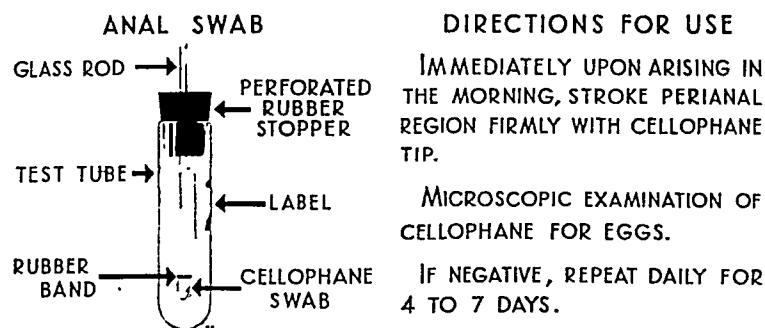


FIG. 4. The construction of the NIH anal swab.

lumen of the appendix is not evidence of their role in causing appendicitis; <sup>2</sup> in fact it is surprising that they are not found oftener in the appendix in view of the high incidence of infection. The pinworm is not known to be capable of invading tissue although it may be trapped within the mucosa by inflammatory reaction.

In infected girls, pinworms may enter the vagina and even wander through the genital tract into the peritoneal cavity producing inflammatory reactions. Single swabs made at the introitus of 45 known cases were positive for ova in 14 instances. Ten of 51 known cases in young girls showed a mucoid vaginal discharge.<sup>2</sup>

Because of the peculiar life cycle of the pinworm, special means must be used to diagnose the infection. Eggs are not commonly found in the stools; in fact when they are found, it is due to chance contamination. In 1937, Hall <sup>4</sup> designed a perianal swab which he called the NIH swab. Figure 4 shows its construction. In use, the swab proper is removed from the test tube and the cellophane tip is stroked along the radiating folds of the perianal region. The square of cellophane is removed from the glass rod and mounted in saline between a slide and cover slip and examined microscopically for the characteristic eggs. Other procedures have been devised for this purpose, such as blotting the perianal region with a piece of scotch tape and examining the tape for eggs.

Frequently a worm will be brought to the physician some hours after its collection. Because of its shrivelled state, it may not appear grossly like a parasite but microscopic examination will usually show the eggs on or within the worm.

There are two important considerations with regard to treatment. First, the infection must always be considered a household infection. Parents and siblings of a known case may become intermittently infected and, unless all are treated simultaneously, the maturation and migration of a single female in an untreated person may reinfect the household. After several

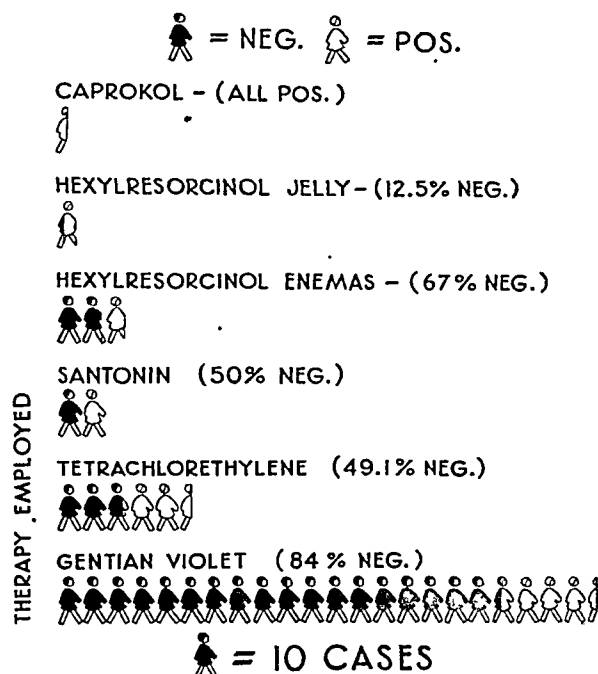


FIG. 5. The results of experimental treatment of pinworm infections with four drugs.

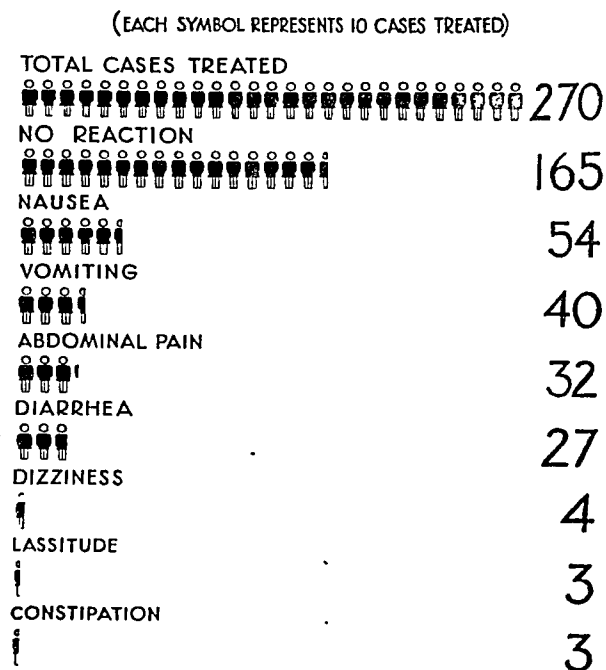


FIG. 6. Reactions to gentian violet therapy.

years of experimental therapy, we concluded that simultaneous treatment of the householders was best in spite of vigorous denials of infection and in spite of negative NIH swab examinations of some members. Secondly, the treatment must be continued over a period of time long enough to insure death of all pinworm ova about the house. In our experience, 23 days has been adequate to accomplish this result.



The drug of choice for treatment is gentian violet by mouth as introduced by Wright and Brady (Fig. 5).<sup>5</sup> Enseals gentian violet tablets (Lilly) probably produce less gastro-intestinal irritation than tablets with other types of coating. The tablets are available in two sizes, the 1/2 and 3/20 grain. The smaller tablets, 3/20 grain, are prescribed at the daily rate of one tablet for each year of apparent age and the larger tablets, 1/2 grain, are prescribed at the daily rate of one tablet for each three years of apparent age up to six tablets (3 grains) daily for adults.

The daily requirement of tablets is distributed into three doses to be taken before meals. Two courses of therapy of eight days each are given with an intervening interval of one week. Patients are cautioned that the stools will be purple-stained and they are cautioned also not to crush the tablets in the mouth because of the staining of the mucous membranes and saliva.

The treatment of pinworms with gentian violet causes some side effects. As indicated in Figure 6, these effects are mostly gastro-intestinal with nausea, vomiting, abdominal pain, or diarrhea. These reactions clear up quickly when the drug is stopped or the dosage reduced. In most cases, the dosage may be reduced to about two-thirds and continued until the prescribed number of tablets have been taken.

We have recommended that serious organic diseases particularly liver and kidney diseases be considered as contraindications to therapy. Alcoholic beverages are contraindicated during therapy lest alcohol-soluble products be absorbed through the intestinal mucosa.

The treatment of pinworm infection in infants is not always satisfactory. Pinworms are not common in children under the age of two but the infection is often acquired by children during the third year of life. In some of these infants, tablets may be swallowed after a training with innocuous tablets and, in some cases, the tablets will be swallowed whole when concealed in jelly. When these schemes fail, resort must be had to treatment with enemas. Evidence is lacking as to whether medicated enemas have any advantage over the use of ordinarily saline enemas. Whatever enema is used, enemas should be given nightly at the hour of sleep for the 23-day period during which the remainder of the household is undergoing specific therapy. During this interval, the migration of a single female may result in the reinfection of the household.

During the treatment with gentian violet, no special hygienic measures need be taken such as have been recommended by earlier writers. In fact, D'Antoni and Sawitz<sup>6</sup> studied control of the infection in

an institution by hygienic measures alone and after six weeks of a strict regimen, the incidence had risen from 38 to 51 per cent.

Although the pinworm is one of the less important pathogenic agents, there is no patient more grateful than the harassed mother whose family you have successfully treated for pinworms.

## TRICHINOSIS

Trichinosis is the most important helminthic disease in the United States. Evidence has accumulated

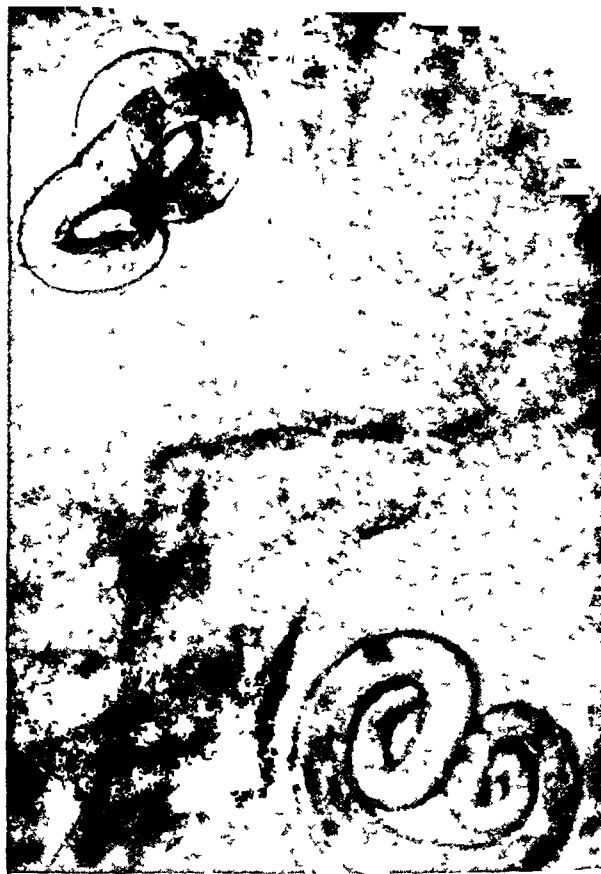


FIG. 7. Cysts of *Trichinella spiralis* observed 36 days after ingestion of infected meat. Magnified about 60 times

that indicates that trichinosis is a common disease in this country and it is probable that the vast majority of sporadic cases is undiagnosed. The largest epidemic that the United States has known occurred during the war due to war conditions. Evidence is not yet available as to whether black market operations in meats have increased the incidence of the disease.

Trichinosis is caused by the small nematode parasite, *Trichinella spiralis*. The adult female trichina bears larvae that find their way to the blood stream.

These larvae penetrate striated muscle where they continue their growth. In voluntary muscle, they lie within the muscle fiber and a cyst wall forms about them as shown in Figure 7. They are now infectious for another animal if eaten. As time goes on, the cyst wall becomes thicker and eventually the host deposits calcium in the cyst wall and the enclosed larva dies. *Trichina* larvae have never been found to encyst in heart muscle, although during the migrating phase they have been found in that location but are either quickly destroyed there or migrate out of the heart muscle.

If viable cysts are ingested by a mammal, the larvae emerge from the cysts and mature within a few days. After fertilization, the males die and the females penetrate into the intestinal mucosa. The adults are found in greatest numbers in the lower small intestine, caecum, and large intestine. The females live for several weeks and have been found as late as eight weeks after ingestion of cysts.

The usual source of *trichina* larvae for man is pork. Bear meat has been incriminated as the cause of several outbreaks. Rats, cats, and dogs have been found infected in nature but their role in perpetuating the infection is probably minimal. The porcine reservoir is replenished by our habit of feeding raw pork scraps to hogs in garbage.

The incidence of clinical trichinosis is unknown. Actually one of each six of us will have *trichina* larvae in our diaphragms at death.<sup>7</sup> The vast majority of these infected persons have had subclinical infections, a few have had mild trichinosis that was not diagnosed as such.

Trichinosis must be considered as an acute febrile disease, self-limited in duration. Mild cases may be ill only for several days. We had the opportunity to investigate hundreds of cases during an epidemic; the severe and moderate cases were readily diagnosed on clinical findings, and in two fatal cases, adults and young larvae were recovered. However, there remained a residuum of many persons who were exposed to the same source of infection and these had a mild illness lasting only several days. These individuals complained of headaches, fever, pain in the muscles, and weakness. Had there not been co-existing cases of trichinosis in the same group, these mild cases would have been diagnosed influenza. It is probable that the majority of mild cases or even moderately ill cases are not diagnosed as trichinosis unless they occur concomitantly with more severe and more easily recognized cases.

The first manifestation of trichinosis in severe cases is likely to be an episode of nausea, vomiting, and diar-

rrhea. This disturbance may subside in a few days or may merge with the symptoms occurring when the larvae begin their migration. These symptoms are mounting fever, headache, and prostration. The fever ranges between 101° and 105° F.; it is more likely to be high in the afternoon but it does not exhibit a characteristic regularity. The daily range is several degrees.

Headache is one of the commonest and most annoying symptoms. The headache is severe and usually referred to the vertex but it may be frontal or occipital. It is not relieved by the usual analgesics.

Prostration is severe and is greater than can be accounted for by the fever alone. If the muscular weakness is due to the myositis from invading larvae, it is likely to be symmetrical but may not involve the arms, legs, and back equally. The muscles are swollen and doughy in consistency and may or may not exhibit resistance to passive motion. Sometimes the muscles may be completely flaccid and the weakness may be such that the patient cannot raise the head or extremity from the bed. The muscle pain has been unduly stressed as a symptom of the disease; muscle pain and tenderness are not conspicuous symptoms and are overshadowed by the weakness. In two cases, we observed a paralysis of the forearm probably due to the central nervous system involvement by the parasites; both cases recovered completely.

In the more severe cases, the symptoms and fever subside by lysis during the third and fourth weeks of illness. Strength gradually returns but there may be a residual weakness for many months afterward. Even a year after the acute illness, we have had patients complain of weakness and dizziness. There is no recurrence of the acute symptoms unless the patient again ingests viable *trichina* larvae.

There are two very valuable signs in trichinosis. Neither is always present but either is helpful in making the diagnosis. Periorbital edema occurs in over half of the cases. The edema is symmetrical involving the facial tissues about the eyes (Fig. 8) and may also appear as edema beneath the conjunctivae. Eosinophilia is marked, even up to 80 per cent, but the eosinophil count may not be elevated in the desperately ill patient. A few years ago, we investigated an outbreak in nearby Virginia. Twelve persons had clinical trichinosis; two others who gave histories of eating the infected meat denied all symptoms but had eosinophil counts of 55 and 56 per cent, respectively.

The presence of subconjunctival or subungual (splinter) hemorrhages should make one suspicious of trichinosis. These symptoms occur in only a small percentage of cases but are valuable when present.

Leukocytosis is generally present and it is due almost entirely to the increase in the number of eosinophils. Stool examinations are not reliable in diagnosing trichinosis. *Trichina* larvae may be recovered from the blood but there is considerable difficulty in finding and identifying them.

The intradermal test with trichina antigen becomes positive three or four weeks after the infection is acquired<sup>8</sup> and the precipitin reaction usually appears at the same time. Experimentally, the complement fixation test has been positive as early as four days after infection.<sup>9</sup> The intradermal test remains positive for years but the serologic tests remain positive for a shorter interval. Positive tests must be interpreted with these facts in mind because they may be positive from previous subclinical or clinical infection.

Muscle biopsies are unreliable as an aid to the diagnosis during the acute illness because the trichina larvae are unencysted and lie parallel to the muscle fibers. Because they may be few in number, a large amount of muscle tissue may be needed to demonstrate the larvae. Three methods of examination of muscle tissue are available and each has its disadvantages. Pressed preparations of unfixed muscle tissue offer the best chance of success but preparations are not permanent. The examination of sediment in a conical glass after 18 hours' digestion with artificial gastric juice at 37° C. may reveal free larvae. Histologic preparations may not show larvae in all levels so that sections should be made at intervals through the block of tissue.

Because of the protean manifestations of trichinosis, the differential diagnosis must give consideration to many of the febrile illnesses. As already noted, influenza may be simulated by the mild cases. Poliomyelitis, brucellosis, and typhoid fever are among the conditions that may need be differentiated from the more severe cases of trichinosis.

The mortality is variable in different outbreaks, dependent for the most part upon the number of viable trichinae ingested. The general appearance of the patient may be misleading because many who seem to be continuously deteriorating will improve and completely recover. Death may occur from a terminal bronchopneumonia or from an aggravation of pre-existing organic lesions. In one case, autopsy

revealed that the immediate cause of death was coronary thrombosis but histologic sections indicated, in addition, an extensive myocarditis attributed to migrating trichina larvae.

There is no chemotherapeutic agent of proved value in trichinosis. It is said that purges are of value but this is probably true only for the interval while the trichinae are in the intestinal lumen and before the disease can be diagnosed clinically. The sulfa drugs and penicillin are ineffective against the trichinae. Treatment is therefore supportive and palliative.

The best prevention lies in the adequate cooking of pork products. For those pork products that are customarily eaten raw, federal regulations require their processing by federally-inspected packing houses to kill the trichina larvae; a similar protection is not always provided in state-inspected or uninspected plants. There is no law requiring processing of pork products that are customarily cooked before consumption.



FIG. 8. Periorbital edema of trichinosis.

## BIBLIOGRAPHY

1. Cram, Eloise B.: Studies on oxyuriasis: XXVIII. Summary and conclusions, *Am. J. Dis. Children*, 65:46, 1943.
2. Ashburn, L. L.: Appendiceal oxyuriasis: Its incidence and relationship to appendicitis, *Am. J. Path.*, 17: 841, 1941.
3. Brady, Frederick J., and Willard H. Wright: Studies on oxyuriasis: XVIII. The symptomatology of oxyuriasis as based on physical examinations and case histories on 200 patients, *Am. J. Med. Sci.*, 198:367, 1939.
4. Hall, Maurice C.: Studies on oxyuriasis: I. Types of anal swabs and scrapers, with a description of an improved type of swab, *Am. J. Trop. Med.*, 17:445, 1937.
5. Wright, Willard H., and Frederick J. Brady: Studies on oxyuriasis: XXII. The efficacy of gentian violet in the treatment of pinworm infestations, *J. A. M. A.*, 114:861, 1940.
6. D'Antoni, Joseph S., and Willi Sawitz: The treatment of oxyuriasis, *Am. J. Trop. Med.*, 20:377, 1940.
7. Wright, Willard H., K. B. Kerr, and Leon Jacobs: Studies on trichinosis: XV. Summary of the findings of *Trichinella spiralis* in a random sampling and other samplings of the population of the United States, *Pub. Health Rep.*, 58:1293, 1943.
8. Bachman, George W.: An intradermal reaction in experimental trichinosis, *J. Prev. Med.*, 2:169, 1928.
9. Bozicevich, John: Personal communication.

# Treatment of Some Intestinal Worm Infections\*

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## HOOKWORM DISEASE

During the past quarter century, hookworm disease has decreased both in incidence and intensity. Evidence indicates that the effects of the disease are more pronounced in the presence of an unbalanced or inadequate diet. Dietary corrections should accompany treatment for the removal of worms. Hemoglobin loss should be combated through the administration of iron since anthelmintic treatment without regard to these factors is only partially corrective.

Tetrachlorethylene is the drug of choice for the removal of hookworms. It is much safer than carbon tetrachloride and is largely replacing the latter drug. The adult dose is 3.0 to 4.0 cc. The dose for children is based on 0.1 to 0.2 cc. for each year of apparent (not chronologic) age. The patient should be allowed a light supper on the evening before treatment. The drug is given on an empty stomach the following morning and should be immediately preceded or followed by an adequate dose of a saline purgative. Fewer disagreeable effects are encountered when magnesium citrate solution is employed instead of magnesium or sodium sulphate. Food should be withheld until after the bowels move. If adequate purgation does not ensue within four hours after the administration of tetrachlorethylene, or if threatening symptoms develop, strenuous measures should be instituted to hasten evacuation and prevent absorption of the drug. In constipated children, a saline purge is advisable on the night before treatment followed the next morning by a high soapsuds enema prior to the administration of the drug.

Contraindications for tetrachlorethylene include gastro-enteritis, alcoholism, chronic constipation, and concomitant infections with *Ascaris lumbricoides*. Syphilitic patients under treatment with arsenical or mercurial preparations are poor risks for tetrachlorethylene therapy. Fats and oils should be withheld from the diet for 48 hours prior to treatment as they add greatly to the absorption of tetrachlorethylene.

## ASCARIASIS

Spread of the large intestinal roundworm, *Ascaris lumbricoides*, is associated with soil pollution in the immediate environment, young children being chiefly responsible for dooryard pollution. Treatment without the correction of defecation habits is only a temporary expedient. *Ascaris* is encountered chiefly in rural areas but children in towns and cities are occasionally infected. For instance, in random samplings among Latin Americans in Tampa, Florida, we found an incidence of 8.9 per cent in 518 children and adults.

Oil of chenopodium is very effective for the removal of large roundworms, but it is extremely toxic and probably has been responsible for more fatalities than any other single anthelmintic. In single doses, *santonin* is not very effective and the best results follow the use of small repeated doses. *Hexylresorcinol* is the drug of choice. This is available in the form of *Caprokol* pills each containing 0.2 Gm. of the drug. The dose for adults is 1.0 Gm. and for children 0.4 to 1.0 Gm., administered in accordance with directions on the container. Care should be taken to see that the pills are not broken or crushed in the mouth as *hexylresorcinol* is a local irritant and may produce annoying burns. Contraindications to the use of *hexylresorcinol* are not well defined but as a precautionary measure it should not be used in the presence of gastro-enteritis or peptic or duodenal ulcer.

## TAPEWORM INFECTION

Infection with the large tapeworms, *Taenia saginata*, *T. solium*, and *Diphyllobothrium latum*, is not frequent. Usually worm segments are noticed in the stools and free eggs may or may not be found on laboratory examination. *Hymenolepis nana*, the dwarf tapeworm, is of more common occurrence and is found more frequently in children than in adults. Surveys in seven southern states during the past decade disclosed an incidence of 1.3 per cent in approximately 450,000 individuals. The parasite occurs less frequently in the north, although we encountered an incidence of 5 per cent in 220 individuals in rural

\* From the National Institute of Health, Bethesda, Md.

Ohio. *H. nana* is difficult to combat because internal autoinfection may occur.

Consistently good results are not to be expected with any of the anthelmintics used for the removal of tapeworms. Regardless of the drug employed, particular attention should be paid to the preparation of the patient. No supper should be allowed on the evening before treatment. At 6 P.M. the patient should receive 15 to 30 Gm. of magnesium sulphate. A high enema may be given the next morning though some authorities recommend repeating the dose of magnesium sulphate at this time. The taeniafuge should be administered on an empty stomach and no food should be allowed until the drug has acted or until the bowels have moved copiously. Best results usually follow where the anthelmintic is administered by duodenal tube. Following treatment for the large tapeworms, the patient should evacuate over a basin of warm water in order that the chain of proglottids or segments may not be broken through contraction which results when the worm strikes cold water or a cold surface. During the period of treatment, the patient should be confined to bed and kept under close observation in order that reactions may be noted and remedial measures may be instituted promptly.

Carbon tetrachloride or tetrachlorethylene may be used for the removal of large tapeworms. The former is more efficient but the latter is safer. Neither is of value against the dwarf tapeworm. For the latter, oleoresin of male fern or kamala may be employed.

The dose of oleoresin of male fern for children varies between 1 and 3 Gm. according to the chronological age. The drug may be given in a capsule and should be followed immediately by a purgative dose of magnesium sulphate. For adults, the method of Magath and Brown<sup>1</sup> may be used. An emulsion is prepared containing 6 cc. or grams of oleoresin of aspidium, 8 Gm. of powdered acacia, and distilled water sufficient to make 60 cc. Half of this emulsion is administered by duodenal tube and the remainder is given one hour later.

Kamala may be given in capsule or in syrup of lactopeptone in a dose of 4 Gm. for adults and 1 to 3 Gm. for children, depending upon the age and condition of the patient. As kamala has a purgative action, no purgative should accompany this treatment unless the bowels do not move in three to four hours, in which case a saline purgative should be administered. Complete removal of *H. nana* by a single treatment is not usually accomplished. Oleoresin of male fern and kamala are contraindicated in febrile conditions, chronic constipation, gastro-enteritis, pregnancy, and in moderate to severe cardiac, hepatic, or renal disorders. In very young children the drugs should be used with considerable caution.

#### BIBLIOGRAPHY

1. Magath, Thomas B., and Philip W. Brown: Standardized method of treating tapeworm infestations in man to recover the head, *J. A. M. A.*, 88:1548, 1927.

## BOOK REVIEW . . .

ALLERGY IN THEORY AND PRACTICE. By Robert A. Cooke, M.D. 572 pages. Philadelphia, Saunders, 1947. \$8.00.

This volume by Cooke and a group of associates contains an authoritative statement of present-day concepts in allergy. Cook's many years of work and his important contributions render this summary of his views significant. He has written, with great clarity, in terms understandable to the clinician, on the immunologic background of allergy.

The book is well organized in sections with separate chapters on theory and practice. The sections on pathology by Klemperer, and immunochemistry by Heidelberger are excellent. The sections on asthma and hay fever are eminently practical and cover all the details necessary for quantitative skin testing and treatment with fractional pollen extracts. A large section is devoted to allergy of the skin with a chapter

on occupational dermatoses by Schwartz. Grove presents an analysis of radical sinus surgery in patients with infective asthma. His results appear good, but this is a very controversial subject with widely divergent views. The section on allergy of the cardiovascular system by Harkavy covers the newer concepts of allergy in internal medicine. Sections on allergens and technics provide detailed information on preparation of materials and skin testing.

Of special interest is Cooke's forthright declaration of the uselessness of skin testing in certain conditions, particularly infantile eczema and delayed types of food allergy; also his disbelief in the leukopenic index.

This book will be accepted as the standard and authoritative work on the subject. It will be useful to all who are interested in allergy but particularly to advanced students and to practitioners who wish to extend their knowledge of the subject.

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## Treatment of the Ambulatory Chronic Cardiac Patient \*

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There are many individuals suffering from chronic heart disease who can be maintained in a state of fair compensation providing they have proper care. Many of these at their jobs today with recognizable but unsuspected cardiac symptoms have not yet consulted a physician. Many others remain at remunerative vocations because of a properly directed living program.

The chronic "cardiac" may be defined as one whose heart from any cause is no longer able to maintain an efficient circulation with adequate reserve. The appearance of breathlessness, easy fatigability, diurnal edema and nocturnal diuresis are the expressions of a fagging heart muscle and evidence of a diminished cardiac reserve. Unless corrective measures are taken the condition ultimately may progress to complete loss of that reserve with the progressive appearance of cough, insomnia, nocturnal "starts," orthopnea, enlargement and tenderness of the liver, cyanosis, ascites, anasarca, hemoptysis, etc.

Treatment of necessity must be modified to properly combat certain etiologic factors. In acute rheumatic heart disease, prolonged bed rest, salicylate saturation and elimination of foci of infection are paramount. In syphilitic heart disease, penicillin and appropriate heavy-metal therapy must be cautiously instituted and continued over a protracted period. The patient with essential hypertension must be taught the art of relaxation and the individual with arteriosclerosis the need for restricted activity. The obese patient should be reduced to a substandard weight and the diabetic patient adjusted to optimal control by diet alone or with insulin. Thyroid administration in myxedema demands caution and in thyrotoxicosis surgical removal of the thyroid gland is an essential to be just as prudently approached. The arrhythmias require intelligent evaluation for proper therapy, pericardial disease demands special surgical measures while chronic pulmonary disease, putting an additional handicap on the heart, necessi-

tates judicious co-ordination of complementary therapy.

There remain, however, certain fundamental principles which definitely set our course in the treatment of chronic heart disease. For the sake of clarity I shall discuss first, the predecompensation phase, second, the decompensation phase and third, the post-decompensation or restored compensation phase. Naturally, these overlap or fade into each other.

We are daily challenged to recognize the potential cardiac patient in the predecompensation phase. He has little, if any, encroachment upon his cardiac reserve, and yet, if we opportunely study him we may anticipate and by proper therapy postpone or prevent the appearance of frank decompensation. Cautious physical activity, adequate rest and diversion and a salt-poor, high-protein diet restricted for optimal weight control will save many from future invalidism. The hypertensive patient must be taught the art of relaxed, unhurried, worry-free living. Worrisome responsibilities and fatiguing activity must be broken by recreational diversions, a regular rest program and more frequent vacations. Adequate sleep of from eight to ten hours daily will do much to restore the energies lost from a day's activity and preserve myocardial efficiency. Dissipating habits must be discarded for temperate living is essential. Promiscuous drinking and alcoholic intoxication are dangerous enemies that easily break down an otherwise adequate heart muscle. Metabolic requirements of the body and, therefore, the heart load can most adequately be reduced by restricting food consumption and limiting physical exercise. Thyroidectomy as a treatment for coronary disease and advanced congestive heart failure is already in the discard, but I believe it is not urged often enough as a prophylactic measure where low grade hyperthyroidism, so easy to overlook, is the background of actual or threatened myocardial breakdown. Thiouracil in our hands is proving to be a most valuable drug in reducing metabolic demand.

\* From the Medical Department of Harris Clinic.

With the appearance of decompensation we face additional problems and our primary objective is reduction of the cardiac load. This is attained first, by minimizing the work requirements of the heart (passive therapy) and second, by removing the existing overload (active therapy).

Minimizing the work requirements of the heart by physical, mental and emotional rest may be called the first principle in the treatment of heart disease. The patient confined to bed should be made as comfortable as possible with the simplest and least upsetting method of taking care of the bowels and kidneys. Voiding is fairly easy to accomplish in bed, but defecation is not. The bedside commode should be prescribed whenever feasible, but I offer the *bed-height commode* as safer, of wider application and much more satisfactory to the patient. It eliminates the emotional tension and the physical strain incident to wrestling with a bedpan. In fact, the bedpan is one hurdle that keeps many a patient in fear of the hospital. Many "cardiacs," if not too severely decompensated, may be permitted to go to the bathroom and this practice should be properly re-established as a means of rebuilding cardiac reserve after decompensation.

Reduction of metabolic activity by a low caloric diet has been shown by Master to be a most effective method of reducing work requirements of the heart. This is simple and should be uniformly employed. Its importance can hardly be overstressed. It is essential that foods be weighed or carefully estimated by measure. While daily food values are held to a low level of 800 to 1,600 calories, depending upon the indications, we must take care that the protein ration does not drop below the minimal daily requirement of 60 Gm. As a matter of fact, recent studies point to the value of high-protein diets in the rebuilding of myocardial reserve. Vitamins are metabolic essentials and the B complex and ascorbic acid especially should be provided over and above the average restricted diet. Subvitaminosis much more commonly is a disease factor than we have previously suspected and added thiamine often will achieve what digitalis alone fails to do.

Adequate sedation is important. While morphine may not be necessary, bromides or chloral or the barbiturates in one form or another can be used to a great advantage for giving adequate rest at night and relaxation during the day. We need not fear the effects of sedatives on the heart. However, we should be alert for signs of toxic psychosis especially in arteriosclerotic persons. When these appear sedation should be limited to codeine or other opiates alone

or combined with aspirin. Codeine may be given nightly for long intervals without fear of addiction. Frequently, whiskey at bedtime is a most desirable soporific. Where barbiturates are not tolerated, 20 gr. of chlorotone at bedtime may give restful sleep. *The cardiac patient must have rest* and the ambulatory "cardiac" is no exception to this rule.

A proper understanding of the hydrodynamics involved in heart disease makes for effective therapy so long as there is a degree of retrievable myocardial reserve. Restriction of fluid intake is a too often neglected essential. Preponderance of fluid intake over output adds to cardiac overload and increases edema. The reverse situation relieves cardiac overload and decreases edema. Fluids, therefore, should be limited to 1,000 to 1,500 cc. daily and once compensation is re-established it is wise to continue this restriction as protection to the rising cardiac reserve. In hot weather when much water is lost through the skin one may be a bit more liberal in fluid allotments.

Restriction or elimination of salt is an essential corollary to limitation of fluids. It has been shown that salt retention plays a prominent role in the production of cardiac edema. If adequate restriction of salt is achieved diuresis will take place with reduction of the sodium ion concentration and relief of thirst. This can be accomplished by a salt-free diet using dependable salt substitutes. EKA salt contains half the sodium content of sodium chloride and, therefore, should be used sparingly. Potassium chloride is too alkaline to be long tolerated. More recently potassium gluconate has given encouraging results. It must be used liberally. If the patient is co-operative he will effectively adjust himself to a salt-poor regimen without substitute seasoning.

Cardiac decompensation means lagging fluid output with resulting increase in the total fluid overload. Right heart failure often may be dramatically relieved by venesection, but except in acute breaks the elimination of retained extracellular fluids by diuresis is more essential. This may be done by quick digitalization giving 1.8 Gm. of powdered digitalis leaf in 24 hours or 1.2 mg. digitoxin at a single initial dose or corresponding digitalis equivalents parenterally. Still more dramatic and striking response often follows strophanthin or ouabain intravenously providing proper evaluation is given to antecedent and continuing digitalic therapy. Other effective diuretics are the xanthines, ammonium and potassium salts, hypertonic glucose in water and the mercurials salyrgan, mercuzanthin and mercurhydrin. The mercurials should be given by vein along with 500 mg. of ascorbic acid as a detoxifying agent and repeated at intervals

of two to five days until not only all demonstrable edema is discharged but all hidden visceral edema as well. Their efficiency is greatly enhanced by giving them during the period of administration of ammonium or potassium salts which mobilize the sodium ions. For quick maximal diuresis, however, I recommend 7½ gr. of aminophylline, 2 cc. of mercurhydrin and 500 mg. of ascorbic acid in 500 cc. of 10 per cent glucose in water intravenously by slow drip. If anuria supervenes a continuous caudal anesthesia up to the sixth dorsal level for three days may bring about diuresis by increased blood flow through the kidneys.

In the individual with secondary hepatic cirrhosis and ascites, urea crystals in dosage of 30 to 60 Gm. daily frequently increases the urine output and makes the need for intravenous diuretics less frequent. Choline and methionine should be given to improve liver function. The oral administration of calomel frequently is of distinct diuretic value in the treatment of congestive heart failure and is recommended, but a word of caution is given regarding its too frequent or excessive use. Purgation for the elimination of edema is a punishment that in this day of efficient diuretics is outmoded and absurd. Paracentesis of the pericardium, pleura and peritoneum are often necessary, but are much less frequently indicated now than formerly because of more effective diuretics. Likewise, drainage of subcutaneous edema by multiple incision or by Southey's tubes nowadays is rarely, if ever, necessary.

The second phase of treatment of the decompensated patient is to rebuild his cardiac reserve. Optimal digitalization should be continuous on a maintenance basis. I once heard a good cardiologist remark that he never gave digitalis to a patient who was ambulatory. This is poor judgment. Many chronic "cardiacs" may be kept in a state of satisfactory compensation and earning a livelihood through the wise use of digitalis and controlled observation. Digitalis may be kept up indefinitely. The maintenance dose ordinarily will be one or two units daily. Do not alternately stop and start digitalis. If congestive failure has once existed it is certain to recur sooner or later. Furthermore, it is detrimental to a heart muscle to be deprived of its digitalis maintenance requirement allowing it to lose any part of its compensated reserve. Frequently, that loss may never be retrieved. Regular use of the circulation time test will aid in directing digitalis therapy. A circulation time of 16 seconds justifies continuing digitalis therapy and one of 20 seconds demands it. A simple fast pulse without congestive failure contraindicates the use of digitalis.

One's choice of digitalis is nonessential as long as the dosage is adequate. Liquid preparations are not

dependable and their effective dosage hard to regulate. Digitalis leaf gives results I have not obtained with the refined glycosides—they seem to lack something. They do offer a distinct advantage for quick digitalization, but for maintenance dosage the powdered leaf in capsule, tablet or pill is preferable except where the effective dose of the leaf causes nausea. Here, one of the refined products should be used. It is a safe rule that if you are familiar with the effective dosage of and get results with any standard preparation of digitalis don't try to change to some product because it presents appealing claims. Besides, it is a wise doctor who considers the cost of drugs to his patient.

Smith and others have proved the distinct value of the xanthines in maintaining adequate coronary circulation. I have found nicotinic acid to have excellent and I believe better complementary coronary vasodilating effects. This may be given orally for long periods, but intravenously as nicotinic acid or as sodium nicotinate it is valuable in coronary insufficiency and hypertensive crises. Cardiac efficiency will be greatly aided by keeping the hemoglobin and erythrocytes at normal levels by the use of adequate iron or parenteral liver extract. The tonic value of vitamin B especially thiamine is also recognized. I have found androgens and estrogens of no positive value.

The question of how long a cardiac patient should remain in bed, when he should be allowed up, what and how much exercise should be permitted are vital to the successful management of his condition. There is an optimal balance between bed rest and activity. It varies from one patient to another and clinical experience alone can teach one these evaluations. Prolonged bed rest is no less a variant from normalcy than is exertion or over-fatigue. On the contrary, rest carries with it factors of safety while activity lurks with hidden dangers. The abuse of excessive bed rest in treating heart disease of all types is a common error of the misinformed physician on the one hand and the fear-burdened patient on the other. The degree and etiology of the decompensation, the presence or absence of valvular defects, coronary insufficiency or thrombosis, the response to digitalis, the co-operation of the patient—these and many other factors will influence the final decision.

Always the resumption of activity should be gradual. We must recognize that prudent exercise alternating with periods of rest is essential to the rebuilding of myocardial reserve and developing compensatory coronary circulation. Do not leave the patient to his own devices but give him a carefully controlled graduated program to be carried out with cautious re-



gard for the dangers of excesses. Any sort of effort that brings on shortness of breath, palpitation or chest discomfort must be forbidden. Regular recreation and diversion are essential not only for their actual value in increasing oxygenation and improving myocardial tone, but in helping to interrupt business responsibilities and temper the strain of daily routine.

Treatment in the phase of restored compensation should be a projection of methods used in the decompensation phase modified to meet maintenance ambulatory needs. We should conduct it much along the lines suggested in the predecompensation phase adhering strictly to a rest-relaxation program. Under no condition should these patients exercise to the point of dyspnea or effort pain. A controlled graduated exercise and recreational schedule should be carried out well within the limits of the rebuilt heart muscle reserve. The patient must learn to estimate his endurance and at all times to avoid fatigue, late hours, dissipation and exertion. Occupational activities and responsibilities must be reduced to a minimum including mental adjustment to his restricted living program. Diet control is essential with adequate vitamins, liberal protein and restricted caloric values calculated to maintain a substandard weight. Be on the alert always to prevent the reappearance of edema. Permanent restriction of salt, the use of a satisfactory salt substitute and limitation of fluids to a maximum of 1,500 cc. in the 24 hours definitely protects against return of congestive failure. Every effort must be made to remove or control probable sources of further myocardial damage.

I wish to briefly touch upon certain common prohibitions that are proscribed for these patients. Caffeine beverages as a rule are beneficial to the chronic cardiac patient rather than otherwise except in the hypertensive—here these should be denied. Alcoholic

beverages are to be interdicted in quantities calculated to inebriate, but frequently the vasodilating influence of a tonic dose of whiskey one to three times daily may be of distinct value particularly in the arteriosclerotic individual. Furthermore, a hot toddy may often relieve the pain of angina more effectively than does nitroglycerine. On the contrary, the vasoconstricting influence of nicotine is undesirable and may be actually dangerous. The average cardiac patient, therefore, is much better off without tobacco in any form. It should routinely be denied to the patient with coronary insufficiency. "Red meat and eggs," so commonly restricted upon the advice of physicians who find albumin in the urine, rather than being harmful are valuable essentials and may be included in the *protein ration prescribed upon a minimum basis of 60 Gm. per day.*

The patient must be told of the early subjective signs of cardiac embarrassment. He should be taught to consult his physician upon the appearance of shortness of breath, effort pain, dependent edema and nocturia. While doing this we physicians must carefully avoid creating states of fear and unjustified anxiety in our patients. Our efforts to protect an individual from aggravating an organic lesion may have repercussions in a greater disturbance from cardiac neurosis. In short, we must show our patient the logic of his knowing how to protect his heart from overwork and at the same time prevent that fear which so frequently may come from the knowledge that heart disease is present. We must teach him to live with his handicap inasmuch as he cannot escape it. Fear and worry, anger and fretting will only aggravate his trouble. Make him appreciate the fact that his heart rather than his ambitions must henceforth guide his activities. Sell him the idea of an unharried, unhurried life.

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### Incidence of Dental Caries Heaviest in Eastern States

Residents of the New England States have twice as many dental defects as those living in the West, South and Central regions, Commander Carl Schlack of the Naval Medical Research Institute told the 79th annual convention of the Pennsylvania State Dental Society meeting in Philadelphia recently. Dr. Schlack pointed out that the startling geographical variation was uncovered in an extensive four-year study made by the Navy.

The survey showed that when they were inducted into the service men from the North Atlantic and New England states had nearly twice as many cavities and fillings per person as those from the West and Southwest. Dr. Schlack attributed these regional differences to the chemical content of the soil and differences of the amount of fluorine in the water supplies. It is possible that eating candy and other sweets is also a factor in these regional variations.

# The Medical Witness in Court: A Symposium

## Expert Testimony

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CHICAGO, ILLINOIS

It is with a variety of emotions that I appear before you to discuss briefly the subject of medical testimony, particularly as it refers to our effort in the Chicago Medical Society to establish a working committee after the manner of the Minnesota plan, the purpose being a desire to serve as a guide and mentor for members of our profession who are called to testify in our courts of law.

May I say to you that it is an honor and a privilege to come before this distinguished company, representing as it does, two great professions, at least one of which has vast influence in shaping policies, local, national and international, by which we live in peace and in war, in prosperity and in adversity.

It was my good fortune in my early years to be associated with a great neurologist whom some of you will remember well, Dr. Oscar A. King, who was for almost seven years my chief. He was versed in the lore of legal and psychiatric discrepancies. This was the period in which occurred the famous Thaw trial and which seemed to mark the beginning of an era when, in cases of major crimes, particularly homicides, a plea of insanity would surely be made.

I am here, not in the character of one who has had large experience as a medical witness, either expert or otherwise, but more as an observer, interested, sometimes critical, sometimes unhappy, in some fear and timidity to present a plan which would be of value to our joint professions and, what is of greater importance, to our patrons, the general public.

Individuals or groups of individuals who offer a personal service to the public—and this refers especially to professional groups—should undergo constant self-examination of the most critical kind, for the purpose of determining whether or not the best service is being rendered in the most efficient manner. Tradition in many groups may become so powerful that any change or suggestion of change is resented and opposed. With the passage of time, social and ethical

changes are bound to occur, to which individuals and organizations must give heed. If this is not done, society for its own protection must find a way to investigate and, where possible, correct any deficiencies that may exist.

These many years, medical men have been painfully aware of and have deeply deplored much of the medical testimony, expert and otherwise, presented in our courts of law. Ways and means of improvement have been discussed, but little progress can be shown. More and more, there has developed a general agreement that we have been very slow to take any action.

In the earlier decades of this century, attention was directed more especially toward cases appearing in our courts, both civil and criminal, in which the question of sanity was raised. This was especially true when an accused person was on trial for homicide. If no possible justification for a crime could be developed, a plea of insanity was promptly forthcoming. If this was not made the first line of defense, it would always be in at the last. So notorious did this practice become that an intelligent public was almost convinced that one could be sane a half minute before and a half minute after committing a premeditated crime.

The state should have the responsibility and is in a position to control, in a great measure, the evidence of medical testimony. Nevertheless, the fact remains that the state has done very little and few attempts have been made to correct existing abuses.

Individual medical men presume to appear in court for the purpose of testifying in any and all forms of medicolegal action, ranging from obstetrics to psychiatry. It is difficult to understand how it is possible for a medical witness to presume that he is equally conversant with all types of medical practice. Is he in court as an expert in radiology? How can he appear later as an expert in surgery? Or, if he appears today as a psychiatrist, how can he hope to qualify tomorrow as an obstetrician? And yet, according to common report, such practices are not of infrequent occurrence. This form of testimony can only pro-

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duce confusion in the minds of the court and the jury. Indeed, it has been said that some testimony is so tainted with bias and partisanship, in its essence it is so contradictory, that judges find it altogether unreliable. Cohn, in an article, "The Doctor in Court," which was published in the *New Orleans Medical and Surgical Journal*, has this to say: "So vast is the range of subjects which require medical testimony that no man should consider himself qualified to give an opinion in more than a very limited field of medicine."

Many of you remember the Thaw trial in New York, where many psychiatrists were called to testify, both for the prosecution and the defense. Men of undoubted ability were engaged, one group searching for evidences of insanity, while the opposing group, just as earnestly, was looking for evidences of sanity. You also remember the verdict which later was sought to be set aside. Tried in Judge Mills' court, this was denied. Judge Mills' review of the case, his prepared statement, his reasons for denying Thaw's release from institutional care, was regarded by neurologists of that day as almost classic.

Later came the amazing period of murders, more or less salacious, with the Loeb and Leopold tragedy the most widely heralded. Here again was gathered for the trial the most notable group of psychiatrists in the land, all under the guidance of skillful attorneys. Those of you who remember this case will recall that again it was, between alienists, a battle royal.

Now comes something new and different. At the turn of the century, or perhaps earlier, marked industrialization of our country began in earnest, and today is an overwhelming fact. With this new situation, this new change in our social structure, a change from an agricultural to an industrial nation, came new problems; difficult problems facing the industrialist, problems of employer responsibility as well as that of the employee—where did the one end, the other begin? Soon came the enactment of the Employer's Liability Law, and definite financial obligations for certain and definite conditions. Also, during this period of wide use of the automobile, the aeroplane and other means of rapid transportation, a tremendous number of accidents have occurred, with the resultant personal injury suits finding their way to the jury room and the industrial commission. It is not strange that sometimes there is disagreement between employer and employee as to the extent of the injury, nor is it strange that there should be differences of opinion between the insured injured and the underwriter who has undertaken the risk. These differences of opinion must all be adjusted. The result has been that, before our very eyes, the importance of the

alienist has given place to that of the surgeon, who repairs broken bones and injured bodies and who testifies to these conditions in our courts of law. We therefore now find the surgeon as well as the internist appearing before industrial commissions and other judicial bodies, offering opinions, expert and otherwise.

The sole aim of the medical witness should be directed toward maintaining a clear issue, to expedite in every practical way the ends of justice in our courts, whose panels are always overcrowded. It has always seemed to me that the problem of the psychiatric witness could be easily solved. If the question of the sanity of the accused is raised, simply have him committed to a state institution, where men are well trained in psychiatry, for a minimum of 30 days for observation. This plan may seem to you so free of complicated machinery that it could only be the deduction and conclusion of a simple mind, but I maintain that justice can and should be attained, not by devious and uncertain methods, but by a certain definite and direct approach.

The historical significance of the evolution of the expert witness is of some interest. About the middle of the fourteenth century, in England there appeared the jury of experts. These were, for the most part, made up of laymen who were neighbors, friends, relatives, all well acquainted with the accused. Before this time, as you well remember, justice in England was administered by crude device. There was the trial by battle, trial by ordeal, by witness, by simple denial, with enough friends to back the denial with their oaths. Following the jury of experts, came the experts called by the court, and, strangely enough, this was followed by the party or partisan experts, as we know them now.

In 1553, judicial attention was first given the expert witness by Justice Saunders when he said, "If matters arise in our law which concern other sciences or faculties, we commonly apply for the aid of that science or faculty which it concerns, which is an honorable and commendable thing in our law, for thereby, it appears that we do not despise all other sciences but our own, but we approve of them and encourage them as things worthy of commendation."

So many reports of irregular medical testimony of one individual testifying in every sort of condition, of gross departure from medical ethics, have come to our office, that action by the Society seemed imperative, with the question of how best to proceed. We have been informed of one medical man in this city who had made 300 court appearances in one year.

It has been suggested, in some instances, that the

expert involved had committed a dangerous breach of medical ethics and could, therefore, be cited to appear before the proper committee for explanation and advice. Proponents of this plan were correct in so far as it concerned only the members of the Medical Society, but it is a lamentable fact that 20 to 30 per cent of medical men in actual practice have no affiliation with any medical society, and therefore are not subject to any of the regulations of its constitution and by-laws. Some of our states do have laws designed to control the abuse of medical psychiatric testimony; some are patterned after the British system. In Britain, the individual accused of a major crime, or a confirmed offender of the law and in whom the defense prefers a plea of insanity, has the immediate benefit of an examination by a committee of experts, unbiased and unembarrassed by expectation of a fee or other reward. They can, therefore, approach the subject in the capacity of a consultant who makes his diagnosis scientifically, unswayed by any other thought than that of giving a correct opinion. If this examination confirms the contention that the accused is of unsound mind, the case is dismissed from further criminal proceedings, thus saving the state large sums of money otherwise spent in prosecution.

Massachusetts has a similar law in effect since 1921, known as the Briggs Law, which is said to operate remarkably well. If question of mental capacity is made, the case is reported to the Department for Mental Disease where examiners, selected by a medical organization in the executive branch of the government, make an examination. In 14 years, more than 5,000 individuals were examined by this group, with a tremendous saving of time and money to the state. Maine has had a similar law in effect for almost 100 years. Colorado has a very simple law, according to Mr. Herman Weihofen. One sentence is as follows: "Upon the making of any such plea of insanity, the judge shall forthwith commit the defendant to the Colorado Psychopathic Hospital at Denver or to the State Hospital at Pueblo, where said defendant shall be under observation for such time as the Court may desire, not to exceed one month." Maryland, New York, Ohio, Wisconsin and Vermont have laws similar in effect but differing in minor details. Illinois has been dilatory in adopting any method by which these abuses of medical testimony could be corrected.

You will remember the daily press in the era of spectacular murders just mentioned, when the cartoonist entered the field with just criticism of the medical profession. Pictured was the bearded alienist, eagerly reading the account of the most recent murder and wondering which side would reach him

first. Can we then complain if the public, your patrons and mine, find themselves in a position to criticize when their desire and inclination is to love and respect? Is it not time that we take steps to clean our house and make our profession one of honor and above reproach? For this purpose, legislation and disciplinary action are only part of the answer, and the individual who finds himself burdened with the responsibility of aiding the ends of justice might well be reminded of the high purpose of his testimony.

In July 1940, the Minnesota Medical Society, during the presidency of Dr. B. T. Adams, selected a group of its members, who in conference with the Minnesota State Bar Association evolved a plan of supervising and regulating medical testimony in their courts. Attempts had been previously made to provide state legislation that would take care of this problem. The results had not proved entirely satisfactory, and their efforts were made to fill in the breach. The plan developed, operated very satisfactorily, probably better than was anticipated, and in the March 13, 1943 issue of the *Journal of the American Medical Association*, there was published a report of the operations of this plan, written by the chairman, E. M. Hammes.

In April 1942, the attention of the Chicago Medical Society was again directed toward the Minnesota plan by Mackay.<sup>1</sup> He described in detail the plan, with an excellent foreword regarding the problems, the frailties, the weaknesses, as well as some reasons for the unshaken confidence of the public in our profession. This, in spite of the fact that in certain and not too few individual cases, the profession has been compelled to bear the odium and the difficulty of explaining and apologizing for men who, through devious manipulation, are able to qualify as experts. This was a very fair and illuminating article. The matter was discussed at length by the Council of the Society. Communication with The Chicago Bar Association seemed to indicate that Cook County's attorneys were interested and the chairman of the Council appointed a committee of three to confer with a similar committee of the Bar Association which would, if possible, work out a plan after the manner of the one in operation in the State of Minnesota. These conferences resulted in a resolution from the committee of the Chicago Medical Society which recommended that steps be taken by our State Society to adopt a plan for the regulation of medical testimony, similar to that of Minnesota.

The House of Delegates of the Illinois State Medi-

<sup>1</sup> Mackay, M. G.: *Journal of American Insurance*, January 1942.

cal Society has been unable to meet this year, so that this action, unanimously recommended by the Chicago Medical Society, has not been finally acted upon by the State. However, the Chicago Medical Society, the Medical Society of Cook County, being an autonomous body, acting through the chairman of its Council has appointed a committee of four to serve as its committee on medical testimony. The specialties in medicine represented in this committee are surgery, roentgenology, internal medicine and neurology. Our plan of procedure is now in the making, and we do not hesitate to use the valuable experience of others, in our effort to develop our own program.

In the first place, the very fact that we have such a committee should have a salutary influence on those who, through carelessness or indifference, might thwart the ends of justice. This has been true in Minnesota and should hold the same in Chicago. We would be happy indeed if the committee were to find itself without employment. We expect to give wide publicity to the existence of this committee and to referred cases. As in Minnesota, it is expected that complaints, and information as to irregular testimony, be submitted by attorneys, judges, medical men and even by the general public to the committee of the Chicago Medical Society. Transcripts of testimony will be made available to the committee for study, and finally it is expected that the committee will call upon members of the profession to assist in its conclusions, depending upon the specialty involved.

Honest differences of opinion are always to be expected and perhaps are desirable. The personal equation must be considered. All are aware of the fact that medical men use different methods of examination and therapy, and, in most instances, achieve the same results. All this should be taken into account, while not failing to remember that fundamentals are always the same.

The results of this experiment in Minnesota have been outstanding, and the satisfaction expressed by so many who are familiar with its operation has been so great, that I felt it would not be out of place to present at this time a few of the expressed opinions coming from the Bar Association of that state. I quote from an article by Mr. Mackay, taken from the *American Journal of Insurance*: "Cooperation by the Minnesota courts has been excellent." The Judicial Council of the Minnesota State Legislature, headed by Associate Justice Royal A. Stone of the Minnesota Supreme Court, is given considerable credit for the launching of the movement by the medical men. Before the committee on medical testimony took form, a series of conferences was held between a special com-

mittee of physicians and representatives of the Judicial Council and the Minnesota Bar Association. All members of the Medical Association were told, after approval by the state organization of the recommendations in a formal report submitted by the special committee, that appointment of a permanent standing committee on medical testimony undoubtedly would have "a very beneficial effect upon the quality of future medical testimony." Word went out also that the new committee would not confine its activities to any particular type of litigation, nor to any particular court. Letters concerning the committee set-up were sent to judges throughout the state, as well as to newspapers, news services and to medical journals. Judges were asked to assist in putting to use the facilities offered.

The response from judges was prompt and encouraging, and the medical association learned immediately that it had enlisted in the cause a powerful ally. Jurists heaped high praise upon the doctors for having taken the bull by the horns. "I think your association is doing such a fine thing that they should be given much credit," wrote Judge Carlton F. McNally of the Ramsey County District Court in St. Paul to R. R. Rosell, the Medical Association's executive secretary. "I am not sure that the medical testimony that was ever given in a case tried before me was dishonest, but once in a while, I have been suspicious that the person giving the testimony was a little careless in his statements. Even that, however, has not happened for some time, and I think perhaps the appointment of your committee and the resultant publicity that your action has had, will have beneficial results."

Judge J. B. Himel of St. Cloud contributed this comment: "This action was a very timely one on the part of the Medical Association, and I can readily see where it may be, in certain instances, of help and assistance to the Court. I can assure you that I will gladly avail myself of the services of this committee if the occasion arises, and I can assure you of my sincere co-operation."

Of interest was the statement of Judge Hugo O. Hanft, St. Paul, senior member of the bench, who said he has expressed himself "very forcibly" on the subject in open Court, with the result that medical experts appearing before him now are very careful in their testimony. "In fact," Judge Hanft recalled, "in one instance when a certain witness had been asked whether he had an opinion as to the cause of the plaintiff's then present, very serious condition and had answered 'yes,' I asked him whether it was 'an

honest' opinion. He gave an opinion then which completely floored counsel. The next witness following, promptly said he had 'no opinion.'"

Judge Hanft used the anecdote as an extreme illustration of what sometimes happens in the courts in connection with medical testimony. "I could readily see how both of those men would have stated as their opinion that the condition of the plaintiff as it appeared in Court, was proximately and directly due to the accident described, which, as a matter of fact, had nothing whatsoever to do with that condition. Counsel promptly dismissed on the merits."

Judge Hanft long has been interested in the problem of questionable testimony, to the extent of having invested his own funds in equipment which makes it unnecessary to rely at all times upon expert testimony entirely. He complains that at one time, there was some question about testimony concerning the reading of x-ray plates, which resulted in his personal purchase of a shadow box which circulates among all of the judges and, at times, goes to the Federal Court. The jurist gave it as his opinion that "The situation is not nearly as bad in our courts, as it was some ten or fifteen years ago, before some of our judges took the matter up with counsel after testimony was in, or at times commented when motions for new trials were made."

Associate Justice Royal A. Stone of the Minnesota Supreme Court, one of the original supporters of the movement, praised the plan very highly in an interview. His approval of the progress which has been made was perhaps best expressed in an address he made to the county officers meeting of the Minnesota State Medical Association some months ago. He said in part: "You have set up a standing committee to which any judge may refer the record of any testimony which he, rightly or wrongly, suspects of being the result of incompetence or falsehood. But there again, it is respectfully submitted, the initiative must not be left wholly to lawyer or judge. Unless doctors take over the whole matter, the effort will be futile. That is because lawyer and judge will be slow to the point of timidity in even suggesting that the testimony of a doctor should be subjected to investigation by his own colleagues."

"The doctor called as a witness becomes pro tempore a medical juris-consult. That function should rule out all bias and tendency to partisanship. The task of freeing medical testimony from all such improper factors and influence, is yours. If, on the witness stand, a doctor violates the standards of his profession, some other doctor is sure to know of it. On the latter rests the initial responsibility for activating the professional attention deserved by the misconduct.

In proportion as that responsibility is not promptly met and properly discharged, the fault will be that of doctors rather than lawyers.

"You of the Minnesota State Medical Association have the credit of being the first to meet the issue, professionally, constructively and practically. The eyes of the whole American Bar and practically of all state judicial councils will be, if they are not now, watching your experiment. You are in sole charge of it. We mere lawyers must stand by to render such aid as may be possible."

The medical point of view seems well summed up in the statement made to the writer by R. R. Rosell, the State Medical Association's executive secretary. He said: "The seriousness of the problem of dishonest expert testimony has been recognized by representatives of organized medicine for many years. Many proposals have emanated both from physicians and lawyers for changes in the law which would eliminate entirely the hiring by litigants of medical experts. Legal authorities who confer with the committee on the new plan of attack, did not, however, favor any movement to change the law at the present time. All of them felt that the existence of the new committee would, if its functions and objectives were well known, achieve a great deal to control the situation in Minnesota."

One of the more refreshing aspects of the Minnesota experiment in attempting to stamp out abuses of medical testimony is the willingness of its sponsors to admit that the problem exists, and their willingness to have the details of the methods they are endeavoring to use receive widespread discussion. Only too often, when groups of one sort or another set up machinery to "police their own membership," the methods employed are cloaked in a self-imposed veil of secrecy. In his report to the State Medical Association, Dr. Hammes declared that the medical societies of neighboring states, such as Wisconsin and Illinois, are manifesting definite interest in the plan, and the inference is that the Minnesota State Medical Association stands ready to give other medical groups the benefit of its experience in attacking the problem.

Should enough of them follow Minnesota's example, the time may not be far distant when complete confidence in the testimony of any physician who takes the witness stand will be commonplace.

Many years ago, Sir Walter Scott said of the three learned professions: "The clergy live by our sins; medical men, by our ills, while the legal profession lives by our misfortunes." If this be true—and I have never heard of its being questioned—I leave with you the thought: This service should be acceptable, should be reasonable, and should be honest.

# Abuses of Medical Testimony: A Remedy

## The Minnesota Experiment

ERWIN W. ROEMER,† Esq.

I should like to summarize what is generally thought about expert testimony in courts by a quotation from a speech recently made by Chief Justice Simmons of the Nebraska Supreme Court when he was discussing some proposed changes in the rules of evidence relating to expert testimony. "The use of expert witnesses testifying to contrary conclusions has in many instances in certain types of cases become offensive to every sense of justice and amounts almost to a public scandal." Those are strong words. That is a denunciation of the abuses of medical testimony, because I think that is what he meant.

I have very often observed cases where there has been obvious perjury, sometimes on one side, sometimes on both sides. And we hear in a rather facetious manner every now and then, "Well, so-and-so won. He had the preponderance of perjured testimony on his side."

There has been a general feeling, certainly among lawyers, and I think the doctors are somewhat of the same feeling, that a charge of perjury is one of the most difficult charges to prove in a criminal court. That is even true where the testimony relates solely to facts, and the obstacles that are in the way of a successful prosecution when you are dealing with a matter of opinion are, of course, almost insurmountable. It is like trying to get rid of a judge on the bench where you have to resort to impeachment. It is so difficult that it is almost impossible of accomplishment.

Every active trial lawyer can take out of the pages of his own experience quite a large number of instances of perjured testimony that he has encountered, and you hardly need the citation of any cases from me. But let me call your attention to a few rather glaring cases that I have encountered.

Very early in my experience, when I was just starting out in the practice of law, I was standing outside of a courtroom one day, at the time when they were still using sensitized glass plates for recording x-ray pictures. I had an opportunity to see the x-ray picture that some experts were discussing outside this courtroom. Apparently they had never seen the picture before, and it was being passed around, and I was allowed to look at it also. It seemed very apparent to me that there was a fracture that was shown in

that x-ray picture. I heard one of these experts say to one of the others, "What are you going to do about that?" He pointed to a place where there seemed to be a fracture. The other fellow hesitated a moment and said, "Well, why can't we call that a defect in the development of the picture? Let's call it a developmental defect."

Well, that was a cunning answer, it was one that might be accepted. Those three experts testified, and were so exceedingly clever on the witness stand that the plaintiff's lawyer in that case might just as well have waived his cross-examination. I can still recall how chagrined he was when he thought he had a clear case of a broken arm to present to a jury, to then have at least two out of three—I do not recall what the third one testified to—testify that what appeared in that picture and what seemed to be a fracture in the arm was merely a defect that occurred in developing the plate. It was very shocking to me as a young lawyer at the Bar, but some of the older men standing around there seemed even to applaud the rather clever answer that the doctor had made in suggesting that sort of escape from what seemed a perfectly obvious visualization in the x-ray picture.

It is just a few years ago that a very well known trial lawyer, whose firm represents a great many large industries in this city, was over defending a case where it was claimed that the dusts were not properly exhausted from the room in which the plaintiff worked, and as a result of it he had developed pneumoconiosis. The plaintiff's attorney put a doctor on the stand, who testified to a clinical examination of this plaintiff, and said that he had found that the man was suffering from pneumoconiosis. There had been an examination of this plaintiff by a doctor in behalf of the defendant, and the plaintiff's attorney noticed that the defendant's attorney had on his side of the table a large envelope containing x-ray pictures. So, without saying "By your leave" or anything else, he reached across the table and picked up the envelope, drew out the chest pictures. He walked up to his doctor, asked him to read the x-ray pictures. The doctor looked at them, also assuming that these were x-ray pictures of the plaintiff in the case, and promptly testified that they confirmed his clinical diagnosis and showed that this man had an advanced case of pneumoconiosis. As a matter of fact, the defendant's attorney in that case had had a broken rib, and on his way to court

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he had stopped to pick up some x-ray pictures of himself taken by his own doctor; and he was, of course, greatly amazed at what was happening before him.

That was a most flagrant case. In fact, it was so flagrant that when I heard it about the courthouse as a matter of gossip I wouldn't believe it: and I called up the defendant's attorney and spoke to him about it and he assured me that it had occurred. I said, "Do you have a transcript of it?" He said, "Yes, I have a transcript of it." I asked him whether I could borrow it. I was still a little skeptical. He loaned it to me, and I assure you that what I have related to you actually happened according to the court reporter's transcript of that testimony.

Yet I am sorry to say that not a thing was done about that horrible example. Everybody seems to be afraid to do anything about it. It is felt that it is more or less of a useless thing. I tried to encourage some action in that case, but I didn't get very far.

Let me give you one more illustration, because I don't want you to think that all the sinning in this field is done by the doctors.

Several years ago I was defending a case for one of the taxicab companies. Some woman had been injured while riding in a taxicab, and she was suffering from an advanced case of tuberculosis. The injury in this case did not involve her lungs, and there wasn't any claim that the tuberculosis had resulted from the accident; but she did have some injuries that she was complaining of, and she was out at the Municipal Tuberculosis Sanitarium. While she was there she had a very acute attack of her primary illness, and as a result she became somewhat conscience-stricken and remorseful and sent for the investigator for the taxicab company. When he came out, she said she had been given some bad news, she wasn't expected to live very long, and she wanted to get this off her conscience. She said her lawyer had been out there and had sent a doctor to make an examination of her, and the lawyer had suggested to her that the doctor would make a complete examination, including a urinalysis; and he said, "Before you give him your specimen, prick your finger and let some of those drops of blood that you get out of the finger trickle down into the specimen."

There was a case where you would surely say something should be done about it, and we tried to do something. He took an affidavit from this woman. I went out later and talked to the patient. I can verify the statements I have made—they are not only based upon what an investigator told me; she told me the same story. When the State's Attorney got the affidavit from this woman, he immediately sent for the principals. It happened that the husband of this

woman, who wasn't too scrupulous, had decided that he could do something about capitalizing this particular experience of his wife, and he had called up the lawyer and the doctor in the case and had told them that unless they gave a considerable sum to him, he was going to support this story at the State's Attorney's office. When the State's Attorney had the doctor and lawyer in his office, they immediately informed him that this was just a shakedown, and they called up the husband in the presence of the State's Attorney. The husband promptly began to make the threats again that he had made to the lawyer and doctor. This episode so angered the State's Attorney that he dropped the matter and there was no prosecution in that case. I was absolutely convinced that the story was utterly truthful.

One of the illustrations that Dr. Hawkinson used reminded me of still another case, which involved a doctor. He had testified in a case where the plaintiff was claiming that she was suffering from St. Vitus' dance. Judge Shurtleff told me, "This doctor, in testifying for the defendant in the case, had simulated chorea, an attack of St. Vitus' dance, so realistically that I thought he was the greatest authority on that subject in this country. He testified that he devoted a lifetime to the study of chorea. To my amazement, the jury brought in a large verdict in the case. I sent for one of the jurors, and asked him what he thought about the case, and how they happened to arrive at their verdict. When he talked about everything but the medical testimony, I asked him, 'What did you think about Dr. So-and-so?' The juror said, 'That doctor testified before us last week in another case, and he testified then that he had devoted a lifetime to the study of the x-ray. We accepted his testimony at that time, but we wouldn't accept it this time.'"

So you can see that these abuses in the presentation of expert testimony are not limited to one side or the other. They are not limited to the doctors in the case—frequently the lawyers in the case are also responsible. And under this Minnesota plan that Dr. Hawkinson has discussed with you, it is the intention not only to have the active co-operation of all the doctors, but of the lawyers as well. As you know, it affects both sides. Every once in a while, the perjury of some doctor who may testify for a plaintiff in the case is exposed, and that hurts every honest plaintiff in a case, as well as the attempted injury to a defendant, because that jury, which at the beginning of its experience may have heard that kind of testimony, is apt to look upon all later expert or medical testimony as of the same kind or quality and to reject it.



I first heard of this Minnesota plan about four years ago. I read a magazine article about it, and I sent it to Mr. King, who was then president of this association. I was impressed with the experiment that they had made there. Mr. King referred this plan to the Committee on Professional Ethics, and a subcommittee of that committee was asked to look into it and they recommended the adoption of the plan. That is a long time ago. I was a member of that Committee on Professional Ethics later, and the subcommittee of the Bar Association that Dr. Hawkinson spoke of decided to write to the president of the Chicago Medical Society and invite a joint conference. We met with this committee that Dr. Hawkinson notified us of: I can tell you that I have done a good deal of work in this field, but the pleasure that I had and the other lawyers had in meeting this committee of the Chicago Medical Society was compensation for any work that we have had in trying to promote this particular plan. We met with a very enthusiastic acceptance of the plan, and much more quickly than The Chicago Bar Association acted upon the plan. We had not only the acceptance of the plan by the committee, but we had the adoption of the plan by the Chicago Medical Society and recommendation of it to the Illinois State Medical Society as well.

I thought that the Illinois State Medical Society had adopted the plan, but Dr. Hawkinson said tonight they did not meet this year and therefore have taken no action on it. I feel certain from what I have heard that the Illinois State Medical Society will join in the adoption of this Minnesota plan.

The Minnesota plan is really simple. I would like to read my statement of what the plan is. Briefly, this plan contemplates that "judges, doctors and lawyers be asked to call to the attention of appropriate committees of the medical and bar associations any conscious deviations from the truth that they may observe in the testimony of such witnesses." The doctors agreed on their part that upon receiving any such complaint, a committee of experts would be impaneled. The importance of that is this: If there are two sets of witnesses testifying to directly contrary facts, it is very difficult for a lay jury or even for a group of lawyers to determine which one is telling the truth. But this group of medical experts that the medical society proposes to appoint to make an intimate study of any of those situations that may develop cannot be fooled; and I think the men in the profession who are called before such committees know that they cannot be fooled. Therefore, that committee of experts will really be a very practical way of handling or attempting to control this prob-

lem. It is very difficult to suggest remedies. Remember that this perjury in the courts has been going on year after year without anything being done about it.

I want to cite an example of such a case. A woman was injured. They were asking astronomical figures in the case, and it had to be defended. We had information that this woman was really suffering from a luetic disease, but we couldn't find any verification for it. We didn't know how we could establish it. But on cross-examination we developed enough information to find out that she had been treated before the accident by four different doctors. She was an Austrian actress, and all of these doctors were of her own nationality, here in Chicago. An investigator was sent out. Each one was very promptly interviewed and each one of the doctors said, "She is one of my own countrywomen; I don't want to say anything about it," and he would refer us to somebody else. We finally found out that she had been in one of the local hospitals, and when a call was made there, all they would tell us was, "Yes, we had such a case, and she was treated in the dermatology department." That is the department that treats these cases. We served a subpoena, and, sure enough, there was not only in the hospital record a complete history showing a long treatment for syphilis, but a letter to her doctor who had testified for her, a neurologist telling about her positive Wassermann test and giving the facts to someone who had been called in as a consultant in the case. That letter was on the top of the file of letters in the courtroom. The judge was very much aroused by it. The testifying doctor denied that he had ever received the letter. The judge was determined to do something about it, and so was the defendant's lawyer. He was asked to present a petition to have the doctor held in contempt of court, and it took him so long to draw it, that I finally drew it and presented it to the court.

That doctor was in hot water. The State's Attorney was called in. The doctor came to me and told me about the struggle he had had in making good in his profession. He was considered a very competent neurologist. He pleaded like no one has ever pleaded with me in a long active experience, not to be too hard on him and not to prosecute the case too vigorously at the State's Attorney's office. He gave me this personal pledge: "If you don't prosecute this any further, I give you my word that I shall never appear in court as an expert witness, that I shall be meticulous in what I say, and the only time I will ever go to court is when I have actually treated a case or when I am subpoenaed and must testify." He didn't keep that pledge more than about four or five

years. The matter was turned over to the State's Attorney, and nothing ever happened in that case.

It is because of experiences like that, that the Minnesota lawyers and doctors decided something had to be done about it, and so they created their own committees to attempt to clean house. It has been found that very frequently—I am ashamed to say, altogether too frequently—the lawyers knowingly present that kind of perjured testimony. Sometimes they suborn it; they are directly responsible for it. Other times they knowingly present such testimony. So the doctors expect of us and we expect all the judges, if they find such a case where they have any suspicion that a lawyer has had anything to do with framing up that kind of testimony, not only to write to the Medical Society, but to call the attention of the Bar Association to the conduct of the lawyer as well.

The Committee on Professional Ethics has recommended that the Bar Association take the following steps to put the plan into operation and make it effective. This will be brief, and it is important, because unless you do something to implement a policy of this kind, you don't get anywhere. You have got to do something about it—not only talk about it and think about it and reason about it, but you have got to go further and do something about it. This is what the Committee on Professional Ethics of this Association proposes to do:

1. To have the Association write a letter describing the plan and informing its members that it has been adopted by The Chicago Bar Association and the Chicago Medical Society. This plan should be sent to all local, federal, and state court judges, including judges of the state Supreme Court, and all the judges of the appellate courts, and all downstate judges as well, since many downstate judges of both circuit and city courts sit in our local courts from time to time. Similar notices should be sent to members of the Industrial Commission and all of its arbitrators.

2. An editorial should be published in the *Bar Record*, explaining the purpose of the plan and indicating that The Chicago Bar Association is determined to co-operate with the Chicago Medical Society to stamp out abuses in medical testimony and to invoke disciplinary proceedings against any member of the Bar who may be charged with presenting medical testimony with knowledge of its falsity.

3. A meeting should be held in the rooms of the Association, at which a speaker for the Chicago Medical Society as well as one for The Chicago Bar Association would give an oral presentation of the plan and invite the co-operation of the members of the

associations in making the plan effective. This meeting tonight is part of that program.

4. The Chicago Medical Society should be notified by The Chicago Bar Association that its Committee on Inquiry, or some other appropriate committee to be appointed or designated by the Association, is prepared to consider any case involving a complaint against a lawyer that he has presented medical testimony in a case with knowledge of its falsity.

Here is the letter that the committee proposes to write to each one of these judges, arbitrators, and members of the Industrial Commission:

Dear Judge:

This is an important joint announcement of the medical profession and the Bar of Illinois pertaining to the administration of justice in those courts and administrative bodies where medical testimony is produced. It is being sent to all judges and hearing officials before whom such testimony might be initially offered or considered on review.

The Chicago Medical Society, The Chicago Bar Association and the Illinois State Bar Association have unanimously adopted the so-called Minnesota plan for the correction of abuses in expert medical testimony in civil and criminal proceedings, in the State of Illinois. The plan has been in operation in Minnesota for several years with results beneficial to the medical and legal professions, to the courts, and the public.

Most judges, practicing lawyers and reputable physicians who occasionally testify as experts, know that in many cases medical testimony is so contradictory as to indicate the witness has consciously deviated from the truth or is so palpably wrong as to indicate incompetence. This plan offers a remedy.

When this kind of testimony is produced, the judge or other hearing official, or the lawyer, or another physician, should write a letter to the medical society giving the name of the offending medical witness, the name and number of the case and where and when tried. A committee of the appropriate medical society will at its own expense and with the assistance of the proper bar association obtain a transcript of the entire testimony and record. On examination of the same this committee may call in specialists in the field of medicine involved. In cases where this committee finds the expert medical witness has testified falsely or was so incompetent as to indicate a willful disregard of his duty as a physician, proper disciplinary action will be taken before the Illinois Department of Registration and Education or otherwise.

Likewise, judges, hearing officials, lawyers and physicians participating in the case will write a similar letter to the appropriate bar association where they have good reason to believe the attorney (naming him) using such testimony did so with knowledge of its falsity or incompetence. The proper committee of the bar association will at once investigate the matter and take appropriate action against the attorney.

I will not read all of it, but let me read this concluding paragraph:

It is earnestly urged that this letter be preserved for ready reference and as a constant reminder of our objec-

tive. Without your co-operation the plan cannot be effective.

Let me say that when I got the statistics for the Bar Association in 1942, I was informed that for 1940 and 1941 the Minnesota Medical Society had a large volume of complaints, and also for the last half of 1941. Then for the first half of 1942, they had not had a single complaint. That doesn't mean that all the abuses of expert testimony have been remedied, of course, but it indicates that the plan is effective and is accomplishing some good.

When this plan was adopted in Minnesota, at the suggestion of Justice Royal A. Stone of the Minnesota Supreme Court, to whom Dr. Hawkinson has referred, he suggested that there be as complete publication of the plan as was possible to obtain, and that was fol-

lowed out. I won't go into the details about that, though I have them here.

I realize, as I have just said, that this plan will not be wholly successful in eliminating abuses in medical testimony, just as in the case of our Bar Association, the Grievance Committee is not able to eradicate all unethical practices among lawyers. However, it seems to me that it is a step in the right direction, and is certainly bound to do some good, and to cause doctors who are professional witnesses to be a little careful about the testimony they give in our courts. Certainly with the active co-operation of the doctors and lawyers, we should have every assurance of success. Accordingly, I would like to ask especially all the lawyers in this group, and the doctors as well, to give hospitality to this plan and to lend it their sympathetic aid.

## Discussion

J. FRANCIS DAMMANN, Esq., Moderator

QUESTION: One of the great abuses that I have encountered has been with the hospital. I think that there are some hospitals in Chicago that have operated for the past few years in a very unethical manner. I notice that the Bar Association and the Medical Society are the only ones involved in this plan. It seems to me that the Hospital Association ought to be included, because that is part and parcel of the fraud, if any is committed. I see no reason why the Hospital Association should be omitted from this plan. I think hospitals should be subject to the same disciplinary action as doctors and lawyers.

DR. HAWKINSON: My thought would be that most testimony coming from hospitals would be through medical men. X-ray records all come by way of the medical men. You subpoena hospitals sometimes, do you not, to bring in their records, and it is difficult for me to see how they could falsify their records. I don't see how a reputable hospital could do so. I happen to be a member of the board of one hospital, and I can hardly imagine such a thing.

QUESTION: Well, we who engage almost wholly in the trial of personal injury cases have run into some very unfortunate experiences with hospitals, and I am quite sure that Mr. Roemer will verify the complaint that I make.

MR. ROEMER: Of course I am as conscious as the speaker is that there are abuses in that field just as there are in the field of lawyers, and of doctors, or of any other profession. I think that one of the happy results of the meetings between the doctors and the lawyers is going to be this exchange of experiences so that we can communicate to these ethical doctors that are here tonight what these abuses are, and get their help in eradicating them. You cannot accomplish all the reforms at once; but I think, as Dr. Hawkinson has said, that usually the testimony from a hospital is presented by some doctor. That is not always true. The abuses that the speaker refers to I am sure will not all

be uncovered by the Minnesota plan, or will not be corrected thereby. But nevertheless, I think that as these meetings continue, we ought to have several good sound experience meetings. I am sure that by this co-operation and by learning what the difficulties are, we can remove a great many of those frictions and those "pains in the neck" that we suffer from constantly, those of us who do indulge in this personal injury trial work.

CHAIRMAN DAMMANN: As I understood the speaker's suggestion, it was that the Hospital Association join with the others, so that in turn the Hospital Association would learn about any improprieties, just as the medical profession would learn through its committee. That was the suggestion, was it not?

ANSWER: That is my idea.

CHAIRMAN DAMMANN: Do you think that would cramp the style of the Minnesota plan?

MR. ROEMER: Not at all.

QUESTION: I don't know what the results of the Minnesota plan have been, because I am left somewhat in the air about it. Mr. Roemer says that there have been very few complaints in the last couple of years on account of perjured testimony by the medical men. I am wondering whether that is due to the fact that there have been some disciplinary proceedings with good results, or whether it is due to the fact that nothing much was accomplished and therefore there are no complaints. What were the actual results of the disciplinary proceedings? Did they get a number of these perjured witnesses out of the profession, or did they just scare them and be done with them?

MR. ROEMER: The answers I had to the inquiries that were made were that in a large number of these cases the medical society had these witnesses in and examined the record. Of course they found in a number of cases that there was, as Dr. Hawkinson indicated there would be,

an honest difference of opinion. It is only where you can clearly demonstrate that there has been a conscious deviation from the truth that some remedy should be applied. And I understand that there have been remedies applied in Minnesota and that as a result it has brought the doctors in line so that their testimony has not been giving cause for complaint in the courts. They have had the very active co-operation of the judges up there, and both the judges and the doctors have said that the plan was working out very effectively.

I also want to make this observation. It doesn't arise with me. But one of the members of the Board of Managers, who met with our committee, stated it was the opinion of the Board that even though no action was ever taken under the plan, the fact that there was such a committee and such a plan in operation would have a salutary effect in keeping some of the sinners in line.

QUESTION: I am not very conversant with the plan, but it seems it is a plan formulated for the purpose of taking care of the ill after it has occurred. I am wondering if it wouldn't be just as well to have the medical association have various committees set up so if you have a case in court that requires expert medical testimony you could refer it to that committee and they would come in court as unbiased and unprejudiced doctors and give their testimony in the first instance. I am asking Dr. Hawkinson.

DR. HAWKINSON: In that event, these men would have to be called in as witnesses, would they not? Would the court call them? Would that be your idea?

ANSWER: Yes.

DR. HAWKINSON: To come in as advisers of the court?

ANSWER: As *amicus curiae*.

DR. HAWKINSON: Yes. That would be following the plan in Britain, where psychiatrists are called in to examine one who has had a plea of insanity. Would that be it?

ANSWER: On that order.

DR. HAWKINSON: In Massachusetts they have such a plan which has been operating for a good many years, known as the Briggs law. For many years this plan has been a "pain in the neck" for me. I have been around as long as most of you here, and I can't remember a time when I wasn't chagrined and unhappy and sorry about some of the testimony that came into the court, particularly from the psychiatrists. As was pointed out, the industrial surgeon now appears much more frequently than the psychiatrist. Testimony of the industrial surgeon is in a slightly different category. The state could easily take care of the psychiatric testimony, by simply appointing a group of three or four unbiased men, who can find out whether that person is insane or not. It is very easy to do so. I don't believe it would be feasible to have a group of lawyers overseeing or policing a courtroom. I don't believe it would do so well.

In Minnesota, when they call in these men who have erred, they are sometimes simply censured, and once in a while one of them is told that over in North Dakota, or maybe Montana or Wisconsin, there is a town that needs a doctor that has his particular talent; maybe this man has made a fizzle in court, so they advise him to move, which isn't a bad idea.

The worst thing that can happen to a doctor is to have his license revoked. They do that in Minnesota, in case of flagrant abuse—they recommend that the license be revoked by the State Board of Examination and Registration.

The fact that such a committee is in existence, and these

men who are testifying in court a good deal know that, and know they are going to be disciplined, I think that is a deterring influence.

MR. ROEMER: Even if you can call in outside experts, or the court can, each side has a right to present his own experts. The court has a right to limit them. There are some of the judges in our courts who do undertake to select a doctor to make an examination where there is a sharp dispute in the medical testimony. And I think it is a very effective way of handling the proposition. But in a long experience I have found great reluctance on the part of the courts to select some doctor.

I think the speaker's suggestion is a very good one, that if we had a competent staff to which the court could turn for examinations and reports in those cases it would be very helpful. I know of a case many years ago where the late Dr. Edwards—I think he was on the staff of Northwestern University—was called in to make an examination. It was a case that involved the question of whether there was a physical illness or an injury that was the cause of this woman's condition. One of the principal things that we hoped that Dr. Edwards would do was to make a thorough urinalysis. It was felt that this woman was suffering from some kidney infection. He made the examination and a report, and when he was asked about the urinalysis he said, "Well, the urinalysis showed there was nothing wrong. I didn't make it myself. I asked the plaintiff's own expert to make the urinalysis, and he reported it to me." Of course, that sort of examination was utterly worthless. That is why the suggestion that if you could have some competent man who really knows what is required in a case of that kind and will not depend on the doctors on either side to make a test, but do the work himself, is very helpful.

There are some judges who are doing very effective work along that line. I was called up by some lawyers the other day who told me the judge had insisted there be an examination. Both sides agreed to an examination by a well-known orthopedic man in Chicago. One of the lawyers asked about him and I said, "I think you are perfectly safe. He is a competent man." The more that is done, the more likely you are to get a sound end-result in the case. You haven't many judges exercising that power yet, and that is why it is so important to adopt this plan and carry it forward. It is just one step, and as you progress you will adopt other measures as well.

QUESTION: Where you have a situation in which it is thought that the medical testimony has been false, and a committee of experts meet to determine it, how are they going to control the examination of the patient, to determine whether or not the testimony of the doctor has been false, from his findings? To what extent would you be able to compel the attendance of that witness for such examination? How has that been handled in Minnesota?

MR. ROEMER: I don't know the solution in Minnesota, but you cannot compel it in Illinois, unless it is a case brought in the United States courts, where the Supreme Court of the United States has ruled that under the new rules the examination can be enforced. Our state court has ruled definitely that you cannot compel an examination of a plaintiff. You have to rely on expert testimony.

SPEAKER: I am prompted to make this observation. The American Bar Association a number of years ago drafted a law that was supposed to be a uniform expert testimony

law, and that law has been adopted in quite a number of states, and it seems to me that that in a measure meets the difficulty that Mr. Roemer suggested. He said the courts without any such law are reluctant to name a disinterested medical expert, someone appointed by the court. But this law that was originally drafted by the American Bar Association has been adopted in a number of states, and it makes it the right of either side in a case to apply to the court, or the court may do it on his own motion, for the appointment by the court of a disinterested medical expert. When that application is made, the court does make such an appointment.

I would say from my observation and sometime experience in the trial of this class of cases that even though the parties themselves would have the right to call their own medical experts, if the judge has appointed a disinterested medical expert and he has taken the stand and testified as to the condition found in his opinion, for the *ex parte* witness to attempt to go contrary to that independent medical expert appointed by the court, he is going to have pretty hard sledding. It seems to me that, like this Minnesota plan, is a step in the right direction toward the compelling of honest medical-opinion testimony, and I would like to see that law adopted in the State of Illinois.

**SPEAKER:** With reference to the appointment of a medical expert by the court, I may say that the federal rules of practice include a provision of that kind. I happened to be on one of the revision committees when that was passed. One of the very first cases that arose, where the defendant requested a physical examination and the President of the Association happened to be on the other side, I was beaten and the constitutionality of the provision was affirmed. But that is the only case that I have known of; it is the only case in my own practice and the only case I have known of, but there are others, I presume, in the federal court, where they have called for the appointment of a doctor by the court. Whether or not it is satisfactory, defendants' lawyers have not seen fit to take advantage of that provision, and so far as it is concerned in practical operation it is of no benefit at all in the federal practice.

So far as the Minnesota plan is concerned, of course, there is no lawyer who can oppose it. There is no lawyer who has any conscience at all but who must be for it, and I think it is a wonderful plan. I think it is entitled to the wholehearted co-operation of the medical profession and the lawyers, and there is only one thing about it, and that is that it must be absolutely, honestly, and impartially administered. It cannot become the tool of any organization or body or clique of persons. It must be administered absolutely impartially and fairly. That is the only chance of anything going wrong with it.

So far as the appearance of medical experts is concerned, it is very difficult to procure them. The men at the top of the profession are loath to go into court. They are subjected to cross-examination by some attorneys in a way that is distasteful, and truly some of them are abused. In that way, it is difficult to get them. Another thing is that it is difficult to get medical experts who fit into the picture. While they may have their medical knowledge, they are unfamiliar with the proceedings in court, they don't understand, and it is difficult for the top men to really make a fair presentation of their case. I think I have found, and I think most defendants' attorneys have found, that some doctors and surgeons, pathologists, orthopedic surgeons,

who have devoted their time to industrial surgery, have qualified themselves so they can more honestly and efficiently point out exactly the thing they are claiming. It is true there have been some doctors who have specialized in that, and I think they are entitled to great credit. If a man is dishonest that is something else, but I think the great rank and file of the doctors who testify are honest, and I think the great majority of cases that are tried are tried honestly. If there are any that are not honest, of course, that is an entirely different matter.

I don't think that we ought to attempt to discourage doctors from becoming experts in court in testifying as to physical matters which they find. It is a great advantage to the court, a great advantage to the jury, and I think in the long run it is productive of justice.

**SPEAKER:** There is less divergence in the conclusions of medical men in workmen's compensation cases than there is in the ordinary public liability cases, and I believe the reason for that is because, first, under the law, the respondents' attorneys compel the examination of the petitioner, and in the second place, because there is a chance for an honest exchange of medical reports between the attorneys, which brings about a closer, more approximate diagnosis between the medical men.

The thought occurred to me, therefore, that in our pretrial conferences, the Bar Association might consider the advisability of incorporating in the program of our pretrial conferences the appointment of a physician who by agreement between counsel would examine the plaintiff. Of course, we cannot compel him—neither side can compel it. But pretrial conferences are informal discussions with a view of settlement, and our records here show, especially during the time Judge Fisher was a pretrial judge, thousands of cases were settled by informal discussions in the judge's chambers. If the two sides expose part of their files to reach an agreement, certainly the attorney for the plaintiff would submit his client for a fair and impartial examination.

The reason I make that observation is this: Very often the plaintiff cannot afford the type of medical testimony that the defendants can. If the plaintiff is honest about it, and the plaintiff's attorney is honest, the plaintiff's counsel would not object and on the contrary would welcome a fair and impartial medical examination. What would be the result of that? First, less litigation, more settlements and fair settlements, and finally, it would discourage doctors, whether plaintiffs' or defendants' doctors, from taking the chance of getting on the stand and exaggerating the testimony, coloring the testimony, because those doctors would know at the time of trial that that particular plaintiff has already been examined by agreement of counsel at a pretrial conference, by a physician appointed by the court.

I just offer that thought as a possible move towards the solution of this problem.

**QUESTION:** I understood the doctor a few minutes ago to say that one of these Minnesota medical experts had strayed from the narrow path. One of the disciplinary actions was to cause him to move to another community, and that was very effective. I wonder about the citizens of the other community.

**SPEAKER:** I want to make some observations on a phase that hasn't been touched upon. That is the reports of roentgenologists on x-ray pictures they have taken, which

are very misleading, and I believe the medical men could adopt a different way. For instance, what I am speaking of is used in government hospitals, where there are roentgenologists. They will take a heart picture, and the write-up will be that the picture fails to show any evidence of cardiac abnormality. That is a part of the hospital record, and is admissible in evidence in government cases without the testimony of the roentgenologist. The lawyer may not have a chance to cross-examine him. That kind of report really means that from the x-ray picture you cannot tell whether there is anything the matter with the man's heart or not. That ought to be stated. The idea is to have the jury believe that that denies there is anything wrong with the man's heart. I have had some of the leading government roentgenologists admit that to be so, under cross-examination. If the medical men would say what they mean, I think that would be a big improvement and would bring out the truth instead of false impressions.

QUESTION: I would like to ask a question, which might be answered by both speakers, and that is the question of definition of what is an expert witness, and, in line with that, perhaps what could be done about the so-called expert who is an expert in every phase of medicine.

DR. HAWKINSON: You have all heard this story—I got it from my preceptor. A doctor was being qualified in court, and the attorney was not very kind to him, and he asked him to define the Island of Reil. That, you understand, is a part of the brain. He said, "Judge, I never claimed to be a geographer. I don't know a thing about geography. I am here as an expert psychiatrist."

I don't know how men can qualify in a half dozen different fields. They just can't do it. It is up to the judge and the jury. Perhaps the jury has little to do about it. I think perhaps Mr. Roemer can tell you more about that. Our point is this: We would like to clean house, and we need help. I don't think the lawyers are altogether free of blame. I am pretty sure they are not. I think they guide our medical witnesses in the wrong path. Maybe our medical men are easily guided. But 20 years ago, the medical profession of Illinois tried to do something about it, and we got no co-operation whatever from the Bar Association. That is also true of other states. I have a resolution here that was presented in a meeting of the Southern Medical Society about ten years ago by a doctor from Norfolk, a resolution urging the Bar Association to unite with them in the adoption of laws by the state that would control medical testimony.

MR. ROEMER: Of course, we are all in agreement that no man can qualify as an expert in all branches of his profession. I gave you the classic illustration of the doctor, now dead, who qualified as an expert in chorea one week and the next week as an expert in the field of radiography. The jury took care of that because they happened to hear this man testify twice in their short experience of two weeks. That doesn't happen very often. Don't forget that the judges can do a great deal about this. That is one of the things we are laboring to get, an effective judiciary that will really take it to heart, make it its business to try to accomplish a sound result in the trial of any case. I was in a judge's court one day when a leading plaintiff's lawyer brought a doctor into his court. The judge said, "Don't put that doctor on the stand. If you get any verdict based on his testimony, I will set it aside. I don't believe him, and I won't let him go on in my court without warning

whoever puts him on—I know he is called by both sides—without warning you that if he testifies and there is a verdict in favor of his side, I am going to set it aside, because I shall believe that it is produced by perjured testimony." Of course, that went awfully far, but judges can handle this situation a great deal better than they do.

I think some of the suggestions that have been made about what may be done on pretrial conferences are good. My experience over in the Federal Court has been a little different. I was in a court the other day which regularly holds pretrial conferences. The judge said, "Of course you will give an examination. That might just as well be arranged at the same time as the depositions are taken of your clients." He said to the defendant's attorney, "Have your doctor there at the same time." He did it as a matter of course. He thought the defendant was not "required to buy a pig in a bag." This coming Saturday my clients are submitting to an examination. I know he has the power to order it.

SPEAKER: I was listening to all the discussion and wondering whether we are attempting a cure or prevention. I don't know where we are trying to draw the line. I would like to suggest that we should try to prevent, rather than to cure. My suggestion would be to try to prevent the harm, rather than to try to correct it after the harm has been done. The way to do it, I would suggest, would be to have available through the medical profession very reputable physicians and surgeons who would be subject to call at the recommendation of the court, to come in and be employed in the case as expert witnesses, who therefore would not be biased in any way. I think where the plaintiff and the defendant get their own doctors, there is a conflict of interests, and medical testimony must be influenced in one direction or the other, and in order to save the time of the court there might be a panel of experts upon whom the court could rely and call almost automatically in the case.

SPEAKER: It seems to me the plan which has been spoken of this evening, practiced in Britain, sounds like an ideal plan, but I don't know, not being a lawyer, whether our judiciary practices here have gotten along to that point or not. This Minnesota plan, it seems to me, in answer to the gentleman who spoke a moment ago, will present, because, speaking from the standpoint of my own profession, I am quite sure that after a very small number of men have been censured by the committee which is named under this plan, other men who are to appear in court will be very loath to undergo the possibility of any such censure as that. Medical men, at least the great majority of them—and I am quite sure that is sure of the other profession—are not particularly anxious to be censured by their own professional brethren, by their professional associations. So I think there is a real preventive force which will work.

MEMBER: The recommendation of the Minnesota plan is that the transcript of the evidence be submitted to an impartial group of doctors, and as you well know, these transcripts sometimes are hundreds of pages long. Do the doctors who review the transcript give their services gratis, or are they paid, and if they are paid, by whom are they paid?

MR. ROEMER: I am a lawyer and I should not speak for the doctors, but the plan contemplates that those services are volunteered by the doctors without compensation and done as a public service, just as many members of this Association are constantly devoting their time to matters of public interest and in the public service.

# CASE REPORT . . .

## Bulbar Poliomyelitis with Eighth Nerve Involvement \*

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In bulbar poliomyelitis any portion of the bulb or pontine area of the brain with its respective nuclei may be affected giving rise to varied signs and symptoms depending upon the location and extent of involvement.

Cranial nerve involvement accounts for the majority of signs and symptoms in bulbar poliomyelitis, and in the recent epidemic of poliomyelitis (1946) five patients with eighth (acoustic and vestibular) nerve involvement were seen, four of which are described here. Previously Hall<sup>1</sup> and Richards<sup>2</sup> each reported cases of bulbar poliomyelitis with involvement of the eighth nerve, deafness, nystagmus and facial paralysis being present. Both patients survived and recovered complete normal function.

The eighth nerve consists of two separate nerves, the vestibular nerve concerned with equilibration and the cochlear nerve, the nerve of hearing. Fibers of the vestibular nerve arise from the utricle, ampullae of the semicircular ducts and saccule, while the cochlear nerve originates in the spiral ganglion of the cochlea. The cochlear and vestibular divisions of the acoustic nerve separate at the ventral border of the restiform body. Here the vestibular nerve penetrates the brain passing between the restiform body and the spinal tract of the trigeminal nerve toward the area acoustica of the rhomboid fossa. The cochlear nerve terminates in the ventral and dorsal cochlear nuclei. Both nuclei are located in close proximity to the nucleus of the seventh nerve (facial) and the sixth nerve (abducens) which are very frequently involved in bulbar poliomyelitis.

The following cases demonstrate involvement similar to a Ménière's syndrome with poliomyelitis as the cause. Whether the symptoms are due to edema and pressure in the area of the nerve or actual minor involvement of the nuclei by virus has not yet been determined.

### CASE 1

J. M., a 14-year-old white male, was admitted to the Contagious Division of Cleveland City Hospital. Three days prior to admission he developed a head-

ache, nausea, vomited eight times that day and had pain in the back of the neck. The following day he continued to be nauseated and vomited frequently. On the third day a fever of 102° developed and he noticed difficulty in swallowing and speech changes. The voice had a lowered tone quality, huskiness and word formation was slow and inarticulate. There was a tendency to fall to the right. On the day of admission he complained of occasional double vision and inability to fix his eyes on one object due to jerking movement.

Examination revealed a well-developed, well-nourished white male appearing acutely ill. Essential features consisted of nuchal rigidity, positive Kernig and Brudzinski signs; the Romberg sign was positive and the patient fell to the right. There was left palatine paralysis and the uvula moved to the right side only, there was a diminished pharyngeal gag reflex and excessive mucus in the throat. In the face front position there was a horizontal nystagmus with a quick component to the right and occasional diplopia. There was weakness of the anterior muscles of the neck. Spinal fluid had 236 cells (lymphocytes 60 per cent, polymorphonuclear leukocytes 40 per cent) and increased protein (Pandy test +++, Ross-Jones +++) .

The patient continued to have a high fever, became irrational and comatose and expired on the third hospital day.

Diagnosis: Bulbar poliomyelitis with involvement of the sixth, eighth, ninth, tenth and eleventh cranial nerves.

### CASE 2

D. S., a 17-year-old girl, fell ill with nausea and complained of a bloated feeling in the abdomen four days prior to admission to the hospital. The next day she noticed a roaring noise in her left ear which sounded like the "surf hitting against the beach." It was very loud, had an explosive onset lasting only three to four seconds and disappeared promptly only to reappear at approximately 45-minute intervals. She experienced some vertigo when the eyes were closed and objects would jerk back and forth if she tried to fix her gaze. She misjudged distances on the stairs, tending to overstep.

\* From the Jack & Heintz Research Laboratories, the Department of Contagious Diseases, City Hospital, and the Department of Pediatrics, Western Reserve University, Cleveland, Ohio.



She was the same on the third day except that the "roaring noise" was experienced with increased frequency.

On the fourth day she vomited once and had a twitching movement in the corner of her mouth on the left side. The left eyelid, nose and left cheek began to twitch. Hearing seemed to be impaired on one occasion for about ten minutes, particularly for conversational voice. The jerking motion and vertigo disappeared.

Physical examination revealed left facial weakness with loss of muscle movement of left lower portion of the face. There were positive Kernig and Brudzinski reflexes, moderate neck rigidity with pain on ante-flexion. There was no nystagmus and hearing was normal. The spinal fluid contained 44 cells, 25 per cent lymphocytes, 75 per cent polymorphonuclear leukocytes, Pandy test ++, Ross-Jones +, protein 50 mg./100 cc.

On the second hospital day examination by the otolaryngologist showed no abnormality of external, middle, or internal ear, and conduction and perception pathways were normal. The patient continued to have occasional roaring sounds in the left ear which gradually disappeared by the fourth hospital day, and facial muscles gradually regained full motion.

Diagnosis: Bulbar poliomyelitis with involvement of the seventh (facial) and eighth (auditory) nerves.

#### CASE 3

N. E., a seven-year-old boy, was well October 13. On October 14 he vomited, had anorexia and developed slight fever. By October 15 the fever rose to 102° F., he vomited five or six times and had pain in his neck. On October 16 the fever remained 102° F., and the patient experienced vertigo on standing. There was a loud "buzzing" noise in his right ear and occasional diplopia.

There was a 20 per cent weakness of right deltoid and right biceps muscle and a stiff neck with pain on ante-flexion. The Kernig and Brudzinski signs were positive. The Romberg sign was also positive and the patient fell toward the right side. There was slight horizontal nystagmus with a quick component to the left. Whispered voice was diminished on the right. Weber tuning fork test was equal on right and left, but Rinne and Schwabach tests for inner ear disease showed diminution on the right. Both ears were perfused with cold water at different intervals and normal nystagmus response was obtained, however, nystagmus was more pronounced on the left.

Spinal fluid revealed 192 cells (77 per cent lymphocytes, 23 per cent polymorphonuclear leukocytes).

Pandy test was +++++, Ross-Jones +, proteins 90 mg./100 cc.

On the second hospital day patient became very ill, irritable, irrational and finally comatose. Fever remained elevated (102° F.). The following day improvement was noted, the fever dropped toward normal and the patient became more alert. The spontaneous nystagmus had disappeared. Perfusion tests were again performed but when the right ear was tested nystagmus was not obtained as should normally occur with such a procedure. Normal response was obtained on the left side.

During the remainder of the hospital course the patient continued to improve and buzzing sounds disappeared and subsequent perfusion tests gave a normal response.

Diagnosis: Encephalobulbospinal poliomyelitis with eighth nerve involvement.

#### CASE 4

D. B., a four-year-old boy, developed headache, malaise and fever on September 8. On September 10 he had trouble in walking, fever was still present and he was admitted to the hospital.

The eyes were normal and no nystagmus was seen. There was bilateral facial muscle weakness more marked on the right side, and weakness of the right quadriceps, right biceps and deltoid muscles. The Kernig and Brudzinski signs were positive; superficial and deep tendon reflexes were normal. The patient walked with a staggering gait; he refused to co-operate for a Romberg test. No tinnitus was present.

Spinal fluid revealed 58 cells (88 per cent lymphocytes, 12 per cent polymorphonuclear leukocytes). Pandy test was + protein 30 mg./100 cc.

Aural examination revealed a normal membrana tympani and high and low tones were heard well. Tuning fork tests for cochlear involvement were all normal. Perfusion tests with cold water failed to show the normal nystagmus response on the right side.

He made a fairly prompt recovery with facial muscles and peripheral weakness gradually returning to normal.

Diagnosis: Bulbospinal poliomyelitis with involvement of seventh, eighth (vestibular), and ninth cranial nerves.

#### DISCUSSION

Symptoms described in the above cases show clearly the division of the eighth nerve into its acoustic branch and vestibular branch. The acoustic disturbances were manifested by diminished hearing for conversational speech and by intermittent roaring noises



which were universally described by the patients as "flowing water hitting against rocks or a beach."

Toomey<sup>3</sup> has classified bulbar poliomyelitis into two groups depending on the portal of entry of the virus to the bulbar portion of the brain. In group 1 are included those patients who have symptoms referable to the vagus nerve first and later involvement of the other cranial nerves. These cases have gastro-intestinal symptoms, swallowing difficulty, speech difficulty and other cranial nerves and medullary portions involved.

The second group includes those cases in which the seventh (facial) nerve is involved first with occasional extension to other nuclei.

Case 1 is clearly representative of this first group with early gastro-intestinal symptoms and extension to other nuclei, sixth, eighth, ninth and vital centers, until death resulted.

Case 2 is typical of the second group with facial nerve and eighth nerve involvement only limited to a small area; extension did not take place, and signs and symptoms gradually disappeared. Here complete recovery of function took place with recovery of the patient.

In cases 3 and 4 nystagmus and vertigo cleared shortly after admission but perfusion with cold water on the affected side failed to initiate nystagmus and vertigo as occurred when the same thing was done on the unaffected side. Thus one may conclude the possibility of disturbance in vestibular nuclei by the disease was so complete that responsive signs no longer existed.

Cases 1 and 4 showed predominately vestibular nerve involvement while case 2 showed predominately acoustic nerve involvement.

### CONCLUSION

Four cases of bulbar poliomyelitis have been presented, which had eighth nerve involvement as prominent symptoms of the disease.

### BIBLIOGRAPHY

1. Hall, George W.: Poliomyelitis, *J. Nerv. & Ment. Dis.*, 48:445, 1918.
2. Richards, Maude: A case of polio-encephalomyelitis, *Proc. Roy. Soc. Med.*, 8:48, 1914-15.
3. Toomey, John A.: Poliomyelitis, the bulbar type, *Am. J. Dis. Child.*, 50:1362-1373, 1935.

### Sydenham on Gout

1. Either men will think that the nature of gout is wholly mysterious and incomprehensible, or that a man like myself, who has suffered from it thirty-four years, must be of a slow and sluggish disposition not to have discovered something respecting the nature and treatment of a disease so peculiarly his own. Be this as it may, I will give a *bona fide* account of what I know. The difficulties and refinements relating to the disease itself, and the method of its cure, I will leave for Time, the guide to truth, to clear up and explain.

2. Gout attacks such old men as, after passing the best part of their life in ease and comfort, indulging freely in high living, wine, and other generous drinks, at length, from inactivity, the usual attendant of advanced life, have left off altogether the bodily exercises of their youth. Such men have generally large heads, are of a full, humid, and lax habit, and possess a luxurious and vigorous constitution, with excellent vital stamina.

3. Not that gout attacks these only. Sometimes it invades the spare and thin. Sometimes it will not wait for the advance of age. Sometimes even the prime of life is liable to it. This happens most where there is an unhappy hereditary tendency; or, even where (without such being the case) the patient has overindulged

in premature venery. The omission, too, of any customary violent exercise brings it on. So, also, does the sudden change from over-hearty diet in the way of meats and drinks, to a low regimen and thin potatoes.

4. When it attacks a person worn out by old age, it is neither so severe as it is when it takes hold of a young man, nor has it such stated periods. They say it is because generally life passes away before it comes to a climax, and also because the native heat and vigour of the body being diminished, it breaks out upon the joints both less regularly and less vehemently. But if it attacks any person late in life, although it neither fix upon its seat so regularly, nor handle him so severely, it still takes its ground by degrees, so as to lay down a law for itself and choose a type. This it does both in respect to the time of the year in which it intends to open the campaign, and in respect to the duration of the fit. Uncertain as are its periods, slight as may be the torture for a few days, irregular as may be its invasion and retreat, it is still gout, and its later attacks are worse than its earlier.

—From *The Works of Thomas Sydenham*,  
Vol. II, p. 123. Translated by R. G.  
Latham.

# Cases from the Medical Grand Rounds of the Massachusetts General Hospital

Edited by LEWIS K. DAHL, M.D.

BOSTON, MASSACHUSETTS

## CASE 18

### ADDISON'S DISEASE

DR. HELEN S. PITTMAN: We are going to show a woman with Addison's disease. I should like to read three paragraphs from Addison's original description of this disease. If anyone remembers his article, he stumbled on this peculiar condition while he was trying to find an explanation for pernicious or Addisonian anemia. I think it is interesting, because if you will think of his description as the story is told and as the patient is presented, you will see once more what extraordinarily good observers the old clinicians were. His article was published in 1868.\*

... The leading and characteristic features of the morbid state to which I would direct attention are anemia, general languor and debility, remarkable feebleness of the heart's action; irritability of the stomach and a peculiar change of colour in the skin, occurring in connection with a diseased condition of the "supra-renal capsules."

The patient, in most of the cases I have seen ... (he reports 11 autopsies) ... has been observed gradually to fall off in general health; he becomes languid and weak, indisposed to either bodily or mental exertion; the appetite is impaired or entirely lost; the whites of the eyes become pearly; the pulse small and feeble, or perhaps somewhat large but excessively soft and compressible; the body wastes, without, however, presenting the dry and shriveled skin and extreme emaciation usually attendant on protracted malignant disease; slight pain or uneasiness is from time to time referred to the region of the stomach and there is occasionally actual vomiting, which, in one instance, was both urgent and distressing; and it is by no means uncommon for the patient to manifest indications of disturbed cerebral circulation. ... This discoloration pervades the whole surface of the body but is commonly most strongly manifested in the face, neck, superior extremities, penis, and scrotum, and in the flexures of the axillae and around the navel.

It may be said to present a dingy or smoky appearance, or various tints or shades of deep amber or chestnut brown; in one instance the skin was so universally and so deeply darkened that but for the features the patient might have been mistaken for a mulatto.

\* Thomas Addison: On the constitutional and local effects of diseases of the supra-renal capsules, The New Sydenham Society, 36:211-239, London, 1868.

Dr. Goetz will present the story.

DR. FREDERICK GOETZ: Miss D., No. 485460, is a spinster of 63, known to have had Addison's disease since 1945, who was admitted here for the third time on March 26, 1947, complaining of weakness and diarrhea of two weeks' duration. The date of onset of her Addison's disease is not entirely clear. She was always considered to be a delicate person. After a thyroid operation in 1930 she believes that her axillary hair, which was then shaved, never grew again. About the same time she began to notice brown "old-age spots" on her face and the backs of her hands. It was not until 1944, however, that she began to notice a generalized darkening of the body, deeper on the elbows, knees and face. About eight months before her first admission here in April, 1945, she began to notice progressive weakness, loss of appetite, and a craving for salt. She had intermittent bouts of diarrhea, lost about 30 pounds in weight before her admission, and noticed that her memory was failing. It was one of the bouts of watery diarrhea which first brought her to the hospital.

On admission in 1945 she was found to be a small, thin, old woman with an intention tremor of the hands. She did not appear acutely ill. There was generalized brown pigmentation of the body, more marked on the elbows, knees, and face. There was very little pigmentation of the mouth; there was, however, pigmentation of the labia minora. Her blood pressure was 105/65, temperature normal. There was, perhaps, some dullness over the left upper lobe, but no râles. The heart was normal in size by physical examination; there were no murmurs. Her white and red blood cell counts were normal, and the urine was negative except for 5 to 10 white blood cells per high-power field.

Her condition changed alarmingly within a day of admission. Her blood pressure fell, she became weak, apathetic, drowsy and refused to eat. She was treated vigorously with aqueous adrenal extract, desoxycorticosterone acetate (DOCA), and intravenous glucose

and saline. She responded well, although her hospital course was long and eventful. She was maintained eventually on a dose of 5 mg. of DOCA a day, a fairly large dose, and in addition took 6 Gm. of salt a day. She was then given pellets of DOCA totalling 825 mg., and oral medication with salt was discontinued. In addition, 150 mg. of testosterone were implanted. At the time of discharge her blood pressure was about 140/90.

She was then followed in the Outpatient Clinic for a year. She was reasonably well and continued a limited existence at home, being up and about around the house, although she rarely went out. Her further treatment consisted only of another implantation of 150 mg. of testosterone. She complained at times of headaches and swelling of the ankles. Her blood pressure remained usually about 140/80.

She was admitted for the second time in April, 1946, because of three days of confusion, weakness and extreme dizziness, as well as stiffness of the neck. In the Emergency Ward her neck was found to be somewhat stiff and she was very apathetic and confused; blood pressure was 160/80. She was considered to be in mild Addisonian crisis and again was treated liberally with aqueous adrenal extract, intravenous saline and glucose. Her blood sugar on admission was 62 mg. per cent. Previously it had never been found anywhere near that low. She responded again to treatment and was discharged after about ten days, without further pellet implantation.

She was then lost sight of for about a year. She continued at home under the care of her family physician, receiving only occasional "pick-up shots," as he called them, of adrenal extract. These were given when she felt particularly weak or had respiratory infection. She had intermittent bouts of diarrhea and these became more frequent and severe in the two weeks preceding admission, whereupon she was advised by her family doctor to return here.

Miss D. entered on March 26. Her physical examination was much as it had been on her first admission in 1945; blood pressure 110/70; pulse about 100; she was not dehydrated; there was no change in the lungs or heart. She was not having diarrhea at the time of admission. However, on the day following admission, her blood pressure again dropped, as it had on the first admission, to about 75/50, temperature rose to 102°, she refused to eat, became apathetic, complained of chilliness. During the second night of her admission she was given a total of 100 cc. aqueous adrenal extract intramuscularly and intravenously, as well as 3 cc. of oily solution of adrenal extract every three hours. She was given 3,000 cc. of fluid intra-

venously, about half of which contained saline. She responded well. Her blood pressure rose and stabilized at about 90/60, and the next morning she felt well and ate a fairly good breakfast. However, it was thought advisable to continue intravenous fluid for one more day. On the third day of admission, she received a total of 1,600 cc. fluid, 1,000 of which contained saline. That evening she again had an alarming drop of blood pressure to about 75/50, and aqueous adrenal extract was resumed. She received 150 cc. that night and the lipo-adrenal extract was continued at the rate of 3 cc. every three hours. The following morning she was more alert than during the night; her blood pressure at times was difficult to obtain, but eventually rose and stabilized at 85-90/60. Her pulse, which was 150 during the night, slowly fell and remained at about 100. Although she felt well, there was thought to be some evidence of myocardial weakness, as evidenced by gallop rhythm at the apex and slight distention of the neck veins. She was digitalized at that time. She has received since the third day no supplementary adrenal extract by injection. However, pellets totalling 325 mg. of DOCA have been implanted. Her blood pressure has remained stable since that time at about 90/60. One further complication has been the appearance of abdominal pain, worse on the right flank, together with a considerable amount of tenderness. This has been interpreted variously as hepatic congestion and possible infection in the right kidney. The urine has shown 10 to 15 white cells for which she has been given sulfadiazine. Her weight had continued to rise slowly since admission until yesterday, when she lost about half a kilogram. Her hematocrit has fallen from 30 per cent, which is apparently her usual level, to about 26 per cent. The electrolyte values during these admissions are charted on the blackboard.

TABLE 1  
*Blood Chemistry*

	SODIUM	POTASSIUM	BLOOD SUGAR	CHLORIDE
	m.eq./L.	m.eq./L.	mg. per cent	m.eq./L.
M. G. H. 1945	132	5.6	109	95-105
	144	2.5	102	
M. G. H. 1946	137	3.2	62	100-91
	130	4.3	79	
M. G. H. 1947	139	5.1	88	104

DR. PITTMAN: Miss D. remembers having been seen two years ago and said she was delighted to be seen again by the doctors. Here is Miss D., who is a blue-eyed woman, with perhaps the slightly pearly sclerae

to which we have just referred. She quite definitely has pigmentation of the folds of her hands. She has quite a lot of pigmentation on the upper trunk with a rather unusual demarcation, as if she had worn a halter bathing suit. There is pigmentation around her mouth, around the vermilion borders of her lips, and some on the upper alveolar edges, from which all the teeth have been extracted.

I think it is interesting that both of these admissions of Miss D. have occurred because of diarrhea and weakness and then 24 to 48 hours after she came into the hospital she has become acutely ill, in crisis or very close to crisis, and then each time we have discovered the presence of a urinary tract infection. As I understand it, that is one of the things which makes Addisonian patients difficult to handle. She was given pellets on her first admission, she was followed in the Ovarian Dysfunction Clinic, and in March following the first admission, which was ten months after the first implantation, she had more pellets of testosterone implanted. When she was in the house a year ago it was not thought necessary to give her more pellets. She was given a return appointment to the Ovarian Dysfunction Clinic, which she failed to keep.

We want to ask Dr. Albright some questions about Miss D. and he has said that he would talk about her.

DR. FULLER ALBRIGHT: If you understand adrenal-cortical function, you understand internal medicine. The trouble is, I don't understand adrenal-cortical function. Like Gaul, it is divided into three parts: the sodium-potassium hormone, the S hormone, and the N hormone.

Of these three, the sodium-potassium hormone is perhaps the most important. It is necessary for life. Its main function is sodium retention; I think that is first and potassium excretion is secondary. I am not altogether certain, however.

The S or sugar hormone is an integral part of the "alarm reaction" mechanism. We believe that when an individual is damaged, the S hormone is excreted in large amounts to bring about the changes that are necessary to combat the damage. You and I under normal conditions probably make very little S hormone. That would indicate, perhaps, that S hormone is indicated only when the Addisonian patient is very sick, and not continuously.

The third is the "N" or nitrogen hormone. It is the one which is very similar to testosterone. It promotes the building up of protoplasm. That is not a life-saving function. To it is due the growth of axillary and pubic hair. As you know, a female with Addison's disease has no axillary or pubic hair or, at least, if you shave it off, it does not grow back, whereas

a male with the disease because of his testicular function does have axillary hair. The 17-ketosteroids, which measure the N function in the female, are practically nil when the female has Addison's disease, whereas they are only low when the male has it. So much for the three functions!

When it comes to therapy, we will divide the patients into those individuals who are chronically ill and those who are in an acute crisis. In treating the chronically ill patients, the main thing is to get them regulated on DOCA to take care of the sodium. Dr. Thorn, I believe, gives his patients DOCA by injection until he has them well regulated and then a certain number of pellets based on the daily dose of DOCA necessary to keep them in sodium balance. I am inclined to spend less time regulating the patient for implantation of the pellets—to use a little guesswork, if you will, about the number of pellets—and to spend more time regulating the patient after the implantation of the pellets. Given a patient chronically ill with Addison's disease, I would be inclined to give something in the neighborhood of five 75-mg. pellets and watch the patient for two weeks. The things to watch are: (1) blood pressure; (2) the cardiac size; and (3) the weight. Then if it is a female patient, I would add one 75-mg. pellet of testosterone to give a little anabolic function. Whether that is necessary or even helps, is one of those things about which it is impossible to say definitely. Theoretically, it should help, and I think it does. I would give no S hormone except in acute emergency. So far, I think there is little that is controversial.

We did not discuss salt by mouth. I think a moderately high salt intake advisable; then if the pellets are too much or too little you can adjust the salt intake accordingly.

Now, confronted with an Addisonian in crisis, I think he needs the S hormone. Two preparations come in solution, one, watery and one, the lipo-extract, in an oily base; the latter is absorbed more slowly. By and large, 1 cc. of the lipo-extract is equal to about 10 cc. of the watery extract, as far as the S hormone content is concerned. If the patient is in acute crisis, the policy is more or less to give as much watery extract as you can get, something like 10 cc. an hour or every two hours. I think that perhaps the lipo-extract is not quite so good as it may not be absorbed by a patient in shock. You want to get him out of shock first, before relying on the lipo-extract.

Then the question is how much DOCA to give the patient. There, you can roughly figure that the salt action of 1 mg. of DOCA is equivalent to about 3 cc. of lipo-extract and about 15 cc. of watery extract.

So, if you are giving 15 cc. of watery extract every hour, say, that is equivalent to 1 mg. of DOCA every hour so far as the salt action is concerned. That would certainly be enough and no further DOCA would be indicated.

I think the tendency is to overdo the sodium factor in treatment. We forget sometimes that the watery extract has any sodium action at all. We usually give sodium chloride intravenously as well.

There is one more thing about the S hormone. If you lack the S hormone, you cannot convert tissue protein into sugar under fasting conditions, but you can convert food protein into sugar. So it is only the starving Addisonian that needs the S hormone to turn protein into sugar. I think an Addisonian patient should never be without food, which means he should have six meals a day rather than three meals.

If you get into a jam by overtreating with DOCA, as we constantly do, mercupurin or ammonium chloride are excellent antidotes.

That, I think, should lead to some discussion. I think Dr. John S. L. Browne, of Montreal, is here. Will you come down and say a word to help me out? Dr. Browne has done a great deal of work on the S hormone.

DR. JOHN S. L. BROWNE: Dr. Albright asked me to say a few words about the treatment of Addison's disease. I am afraid that I cannot add anything in that respect to what he has said. I think I would like to mention the possibility which has already been suggested by Dr. Nathan Talbot that these three functions which Dr. Albright mentions may not necessarily fail at the same time in the course of the disease. After all, during the course of atrophy or destruction of a gland, the gland is not instantaneously destroyed and there may be variations in the rate or the degree to which these functions have been reduced. One remembers in the early days when salt therapy was used as a method of treatment, one went along some considerable period of time and then the individual might go into acute hypoglycemic crisis and die.

Dr. Albright has said that the S hormone, he feels, is perhaps only produced in large quantities in acute illness. I would not agree entirely with that. I think that the studies which we have made with regard to the excretion of this type of substance in the urine indicate that people who rest in bed have a considerably more constant and lower excretion than people up and around, and that certain individuals who go on a three-mile route march show a very marked increase in the hormone. Perhaps you would regard a three-mile route march as acute emergency or illness, I don't know. However, I am of the opinion that the

S hormone is continuously produced and that even fairly moderate degrees of stress can cause increased requirement, though perhaps not to the extent that it would place an Addisonian in acute collapse.

Now it was mentioned that this lady had a urinary tract infection. We have not done any assays on Addison's disease patients with such infection. We have done them in cases of individuals with pan-hypopituitarism, who ordinarily show, just as most Addisonians do, none of the active glycolytic corticoids in the urine. One patient with an acute pyelitis, with a temperature of 100–101° F., put out approximately 27 glycolytic units. The normal for adult females is 25–65 units, according to Dr. E. H. Venning, and a normal individual with an acute infection puts out 100–200 units. So this individual, who ordinarily put out none that we could detect, under the stress of the infection put out just the lower limit of normal. Ordinarily, she went into hypoglycemic crisis quite rapidly on starving. She had not eaten anything for three days and was vomiting, but the blood sugar was 76 mg. per cent on admission. The infection produced enough adrenal cortical stimulation to keep her from going into hypoglycemic crisis.

As regards this question of different rates of loss of function of cortical hormones, we saw a patient of Dr. K. Paschke's recently who had a typical Addisonian appearance, including pigmentation and electrolyte disturbance, but he did not show markedly increased insulin sensitivity, and he had 29 glycolytic units of corticoid in his urine. Here is an instance where the carbohydrate function of the gland was not so much impaired as the electrolyte. As Dr. Albright has suggested, you can divide adrenal function into three main groups. No one knows why one function should fail more than the other. As the gland continues to be destroyed, at a certain point, the function falls so far that the person gets into difficulty, even though he may not be having acute infection. All I can do is say simply that the question of the treatment of a case of Addison's disease would not remain the same over a period of years as the disease progressed, and we don't know at what point in the degree of lowering of adrenal function, or any one of these three functions, that collection of signs and symptoms occur which has been labeled with this label of Addison's disease.

That is one of the difficulties we are constantly meeting in dealing with syndromes which have been established prior to the increased understanding of pathologic physiology we now have. You establish a syndrome based upon clinical signs and symptoms and autopsy findings, and then you find evidence of varia-

tion within the syndrome. It is no use calling it another syndrome because it has one or two symptoms or signs more or less than the original syndrome. You get into a dreadful mess. I hope people will not invent new names for Addison's disease without hypoglycemia or with it, because I think fundamentally the physiologic process is the same.

DR. PITTMAN: Thank you, Dr. Browne. I think we have used up our share of the time. Do you wish to say anything, Dr. Butler? We still have a minute.

DR. ALLAN M. BUTLER: No. I wonder why one resorted to implanting pellets of testosterone rather than giving testosterone orally?

DR. PITTMAN: Do you want to answer that, Dr. Albright?

DR. ALBRIGHT: Methyl testosterone increases the creatine excretion in the urine and is not quite so good as testosterone propionate. The pellets are cheaper, too.

DR. NATHAN B. TALBOT: Could I ask a 30-second question?

DR. PITTMAN: Yes, indeed.

DR. TALBOT: It is known that the administration of DOCA and sodium salts tends to produce a potassium diuresis and a retention of sodium. As a part of this action, the concentration of potassium within cells falls while that of sodium tends to rise to abnormal values. Apparently as a result of the lowered intracellular potassium concentration, there may develop necrosis of heart muscle and muscular paralysis. How much risk is there of inducing these types of change in the patient with Addison's disease during therapy with DOCA and sodium salts?

DR. ALBRIGHT: With testosterone?

DR. TALBOT: No, with DOCA. During the initial few days or week or so of therapy for this patient, the emphasis has been on sodium chloride and DOCA. For the reasons outlined above, need one worry about decreasing the potassium in cells and serum?

DR. ALBRIGHT: I notice here that the serum potassium level fell to 2.5 m.eq./L. I think you ought to watch the potassium. This patient was obviously over-treated, though. I think there is some danger, but not very great, if you keep within moderate limits.

DR. PITTMAN: There have been very marked changes in the electrocardiogram of Miss D. in two years and I wonder if Dr. White would like to say anything about that? Both those electrocardiograms were taken at essentially the same potassium level, namely, 5.6 and 5.1 m.eq./L.

DR. PAUL D. WHITE: This one taken in 1945 shows apparently normal T waves, in contrast to this recent one, in which the T waves are very abnormal, so it is

obvious that that fact alone is not the only one to influence the electrocardiogram.

DR. TALBOT: Dr. Butler, is it fair to say that the serum potassium is not a very reliable index of intracellular potassium?

DR. BUTLER: What Dr. Talbot is suggesting is important. In Addison's disease there is an elevation in the serum potassium associated with a diminished ability of the kidneys to excrete potassium. I am not sure that we have definitive information as to what happens to the cell potassium. DOCA therapy increases the renal excretion of potassium, lowers the serum potassium, and particularly if sodium chloride is being administered, simultaneously results in decreasing cellular potassium and increasing cellular sodium, as just remarked by Dr. Talbot. Apparently it is this disturbance in cellular composition that results in the muscular weakness that may accompany such therapy. In familial periodic paralysis and in certain patients with renal disease, there is also a decrease in serum potassium which is apparently accompanied by a decrease in cellular potassium. In both DOCA therapy, familial periodic paralysis and these particular nephritics the electrocardiogram shows characteristic changes. On the other hand, the fall in serum potassium which we showed may occur with testosterone therapy† is the result of potassium going into the cells. Under this circumstance the serum potassium may fall to almost zero without the appearance of any of the symptoms of muscle weakness or without the changes in the electrocardiogram. Thus, the concentration of serum potassium is not an index of cellular potassium or the likelihood of muscle weakness, whereas the electrocardiographic changes appear to reflect changes in cellular potassium not serum potassium.

#### *Editor's Follow-up Note*

This patient was discharged on the 19th of April, 1947, after having weathered another mild Addisonian crisis during the week following her appearance at Grand Rounds. Before discharge two 75 mg. pellets of testosterone propionate were implanted in the left thigh. She was discharged on a program which included 4 Gm. of sodium chloride per day with three intermediate feedings and no DOCA injections. On a follow-up visit on the 12th of May her blood pressure was 140/84. She felt well but was found to have very mild edema of the ankles. Her salt was decreased

† Butler, Allen M., Nathan B. Talbot, and E. A. MacLachlan: Effect of testosterone therapy on concentration of potassium in serum, *Proc. Soc. Exper. Biol. & Med.*, 51:378, 1942.

to 3 Gm. a day but otherwise her program was maintained as on discharge.

### CASE 19

#### RHEUMATIC HEART DISEASE WITH ? APPENDICITIS

DR. EDWARD F. BLAND: This case we have known intimately for about 13 years. On two occasions she has

in games she tired in a few minutes, but did not become short of breath. She finished high school and took a full-time job as a stitcher in a garment factory.

Early in January 1946 she began to note a slight nonproductive cough and some undue fatigue. About two weeks later around four o'clock in the afternoon, the cough became quite noticeably productive of yellow sputum streaked with blood. She became nause-



FIG. 1. January 27, 1946.



FIG. 2. February 2, 1946.

presented rather puzzling complications. We would like to present these two complications because we believe in retrospect we understand them.

DR. FREDERICK C. GOETZ: Mrs. F., No. 32559, is a 23-year-old woman of Italian descent who was first admitted to the hospital about a year ago with complaints of cough, sputum and shortness of breath for seven years. However, she has been known to the hospital since childhood. A note in her record, dated 1931, mentions "congenital heart—mitral." She lists no acute illness in her childhood, however. She did not have scarlet fever. She recalls no joint pains, nose bleeds, or abdominal pain.

In 1945 a visit to the Rheumatic Fever Clinic revealed mitral systolic and diastolic, and aortic diastolic murmurs, with normal rhythm. Her life had been entirely normal otherwise until January 1946 except that she had always tired rather easily. Even in school she had not been allowed to participate in athletics. She found that if she tried to participate

ated and vomited. She felt feverish and chilly but did not have actual shaking chills. About six o'clock she complained of diffuse, vague, anterior chest pains. About eight o'clock she suddenly became quite short of breath, which increased over the following two hours. About ten o'clock in the evening she was brought to the Emergency Ward. When she entered she was found to be in severe respiratory distress with a rate of 36 respirations per minute. She was pale, her skin was cold and moist, and her lips somewhat cyanotic. Her blood pressure was 100/60. Her temperature was 101.6° by rectum and her pulse was 100. The eyes showed definite petechiae in the conjunctivae. The neck veins were not distended. The lungs showed perhaps a moderate dullness over the right upper lobe anteriorly, where there were increased breath sounds. There were many fine râles throughout both upper lobes. The heart was thought to be enlarged to the right and to the left. There was a mitral diastolic thrill, and there were loud mitral

systolic and diastolic murmurs, but no aortic murmurs were heard at that time. There was no peripheral edema. The abdomen was negative. The white blood count was 15,000 and the hemoglobin was 14 Gm. The urine was negative.

DR. BLAND: That was January 1946. This woman was in a serious condition with fever and acute pulmonary edema. She was a known rheumatic with old rheumatic heart disease. There was some uncertainty at the moment as to just what caused this trouble. We present her because it is a fairly common complication in young women with a tight mitral stenosis. Perhaps we might see the rather striking x-rays if Dr. Robbins would be willing to comment on them. This was filmed in 1945 when she was in reasonably good health.

DR. LAURENCE L. ROBBINS: This is a fairly characteristic appearance of pulmonary edema with more or less butterfly areas of increased density in each lung field. This film was taken on January 27, 1946. On February 2 the lungs were clear. The heart had much the same appearance on February 2 that it did in March 1945.

DR. BLAND: We simply want to emphasize this very rapid change in her pulmonary state. It was a very acute and very serious situation. Dr. King, you were visiting on the ward at this time. Have you any comments about the diagnostic discussions?

DR. DONALD S. KING: Well, she had this story of a chill and high fever when she came in. On the basis of that and the clinical analysis, I thought she probably had pneumonia or infarct. Then it cleared so rapidly I did not see how we could call it either. I discussed with Dr. Robbins at the time whether chills and fever could be caused by pulmonary edema alone. We had quite a lot of discussion about that as to whether this whole thing could be put on the basis of just pulmonary edema.

A PHYSICIAN: Was the fever very transient?

DR. BLAND: 103° for two days.

DR. KING: Clinically she cleared up in two days.

DR. JAMES H. MEANS: No sign of any active rheumatism?

DR. KING: No.

DR. PAUL D. WHITE: Dr. Goetz referred to the sputum as being yellow. Was it purulent? I would not suppose it would be purulent in an attack of acute pulmonary edema.

DR. BLAND: Do you recall the sputum?

DR. KING: I do not remember it.

DR. BLAND: I do not either. This pulmonary congestion cleared very quickly. This is an acute situation which some of us who follow a large group of

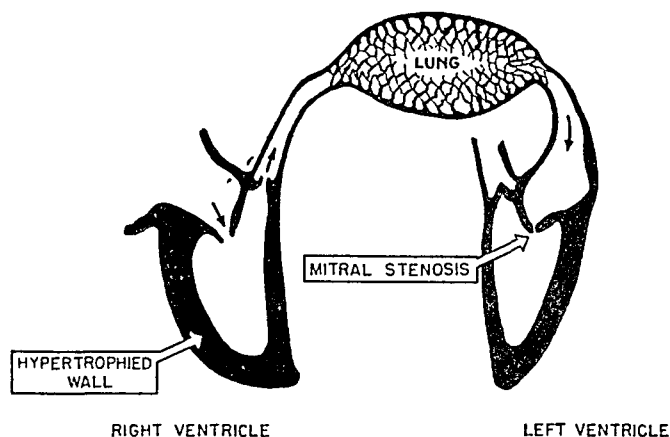


FIGURE 3.

rheumatic patients see fairly often. We recognize certain factors which favor its occurrence. It is more apt to occur in women at the time of their periods. That is rather striking. Any circumstance which increases the heart rate considerably is apt to bring on this acute pulmonary edema, and paroxysmal auricular tachycardia quickly throws these people into a serious state of congestion.

DR. MEANS: Had there been a suggestion of that a year ago?

DR. BLAND: No, not of ectopic tachycardia. When we went into the history of this girl, we found that she had always led a fairly quiet life, but that because of special circumstances she had become considerably more active in the two or three days preceding admission. Her brother was getting married, and there had been a number of feasts and celebrations. She had stayed up late the night before this happened and it was at the time of her period. She was not aware that she had a cold or infection, but that seems a possible additional factor. The following sequence is probably responsible for the acute congestion of the lungs.

Here (Fig. 1) is a simple diagram in which the two sides of the heart have been separated, with the lungs between. The "tight" mitral stenosis results in (1) right ventricular hypertrophy and (2) a restricted outlet from the lungs. Over a period of years the right ventricle became stouter than usual. This patient had right-axis deviation in her electrocardiogram which goes with hypertrophy of the right ventricle. In this respect her heart is too good in that the right ventricle is too strong. The outlet from the lungs is restricted by the mitral stenosis. On any occasion when the heart rate suddenly increases, perhaps doubling its rate, there is only one possible event that can happen. The lungs become acutely congested when the overactive strong right ventricle beats too fast, thereby



pumping more blood into the lungs than can escape through the tight mitral ring.

Digitalis is most unsatisfactory in this situation since it is not primarily heart failure; it is a mechanical imbalance. However, we usually give digitalis, but with a normal sinus mechanism which is most often present under these circumstances digitalis is not very satisfactory in controlling the heart rate.

There is one event which we ordinarily consider a step downhill for most rheumatics but which does seem to benefit these people, namely, the onset of auricular fibrillation. The explanation we do not know. Perhaps there are two possibilities.

One, in the presence of auricular fibrillation one can usually control the heart rate by the use of digitalis in contrast to the difficulties noted above with sinus rhythm. A second possible factor is that perhaps the fibrillating auricles serve as a distensible reservoir to take up the added load on the lungs.

In summary, we present this patient's history as an example of one of the acute emergencies which we see in patients with mitral stenosis. As to treatment we give these people digitalis not hoping for a great deal of benefit. We advise particular caution at the time of their menstrual periods. That is the time when they are more apt to wheeze and to have blood streaked sputum. In the last few years we have put most of them on a low-sodium regimen. They seem to benefit by that program. For the acute emergency, tourniquets and oxygen are indicated in addition to morphia. Mercurial diuretics aid in clearing the lungs.

On one or two occasions when we just happened to be present, we have used artificial respiration. One of the patients in particular, we thought was dead. She had drowned so to speak. But she finally responded to artificial respiration and some months later auricular fibrillation ensued. That was ten years ago. Since the onset of fibrillation she has not had a single episode of acute pulmonary edema.

DR. MEANS: Would you be willing to speak of hypertension with acute pulmonary edema?

DR. BLAND: With hypertension acute failure of the left ventricle occurs. The same thing may happen with acute myocardial infarction. Outflow from the lungs is hindered under these circumstances by weakness and failure of the left ventricle. The acute effect on the lung is exactly the same, however.

DR. WHITE: I think most of them recover even from the immediate attack. The prognosis is very much better than in any other type of acute pulmonary edema due to heart disease.

This patient of ours of whom Dr. Bland has spoken

is not too well, but she is carrying on fairly actively. It is considerably over ten years since she was in the hospital with acute pulmonary edema. She has permanent fibrillation, well controlled by digitalis and has had no serious attacks since that time. We have seen quite a few patients of that sort.

DR. BLAND: This was 14 months ago, when Mrs. F. was so sick and Dr. Goetz will tell us of her subsequent course and the second complication which presented some difficulties recently.

DR. GOETZ: Mrs. F. felt quite well on discharge from the hospital a year ago. She was advised to keep on taking digitalis for about one month. Then it was discontinued. She stayed on restricted activity at home for about two months. Then in April 1946 she was married. She continued to feel well, but she found that she had some shortness of breath on climbing one flight of stairs and had to do this slowly in order to avoid unusual discomfort. In October 1946 she was found to be pregnant. She was estimated to be about three months along and she was referred to another hospital where a therapeutic abortion was performed as well as sterilization. The appendix was not removed.

Following this operation she continued to feel well and she resumed her old job as stitcher. With each period she began to notice a somewhat aggravated choking cough without sputum. In December she complained of palpitation. She was examined in the Cardiac Clinic where she was found to have auricular fibrillation, so digitalis was resumed.

She entered the hospital again on February 24, 1947, complaining of abdominal pain of five hours' duration. Her last period had finished on the day before entry and with this period she also had an aggravating choking cough as well as some nausea and vomiting. With the end of the period she had again felt well and was able to take solid food; the following morning she had quite severe abdominal pain somewhat more severe in the right lower quadrant, which grew steadily worse. She did not vomit, however. On admission to the Emergency Ward at seven o'clock in the morning she was in acute distress because of the abdominal pain. Her respirations were 16; her pulse was 62, and the cardiac rhythm was grossly irregular. The neck veins were not distended or pulsating, and the lungs were clear. The heart was as described previously. However, there was definite abdominal tenderness perhaps somewhat greater on the right side and greater in the right lower quadrant, where there was considerable spasm as well.

Rectal examination revealed diffuse tenderness but no masses or fluctuation. The white blood count was

8,000, rising to 15,000 the following day. The urine and other studies in the Emergency Ward were negative.

DR. BLAND: Another troublesome complication in rheumatic patients is abdominal pain of one sort or another. Occasionally it simulates acute appendicitis exactly. Sometimes it is acute appendicitis. I believe that when this patient came into the Emergency Ward if she had not been a known rheumatic no other diagnosis would have been considered seriously. She had nausea and vomiting, generalized abdominal pain later localizing in the right lower quadrant in which place she was moderately tender, with spasm, and also she had a mild fever and leukocytosis. Because of the rheumatic background there was some hesitation. She began to get well thereafter so promptly that when the diagnosis seemed more definite later, it seemed unwise to do anything surgically about it. Unexplained abdominal pain is more often encountered in the younger rheumatic group. On occasion one cannot make a definite diagnosis on physical examination or by any other clinical means. In general, we believe that when one cannot be sure, it is probably best to explore.

In retrospect, we believe this young lady had acute appendicitis and not a rheumatic abdomen. Things have quieted down very nicely. It took several days for her abdomen to become completely normal and there was diminishing residual tenderness in the right lower quadrant for three days. This has now disappeared. Rheumatics usually do not subside with localization in one part of the abdomen or the other over a period of days. They puzzle one only at first glance.

We have presented this lady because of two puzzling complications, one of which was very serious and the other was potentially serious. We hope she may have no further abdominal symptoms. I would appreciate Dr. Jones' comments about the question of her management at this stage. Would you be content to let her go home under observation? We do not like to operate on rheumatics unless we are forced to.

DR. CHESTER M. JONES: Because you feel you are still up against the problem of stirring up acute rheumatic fever? It is the same old question of choosing between risks, isn't it? Probably your best bet now is the conservative attitude, to sit on it, rather than even contemplate elective surgery. I should think if she had another attack your hand would be forced.

DR. BLAND: Yes.

DR. JONES: It is quite possible that with this attack she may have sealed off her appendix enough so that she will not be bothered any more. I think you

should put that diagnosis in a compartment and open the door if anything happens.

DR. BLAND: That is our attitude at the moment.

DR. MEANS: Have you ever seen a rheumatic appendix?

DR. BLAND: No, we have not. We have taken out many an appendix during rheumatic fever for abdominal pain. Sometimes it is acute appendicitis.

A PHYSICIAN: How many attacks are due to mesenteric embolus with the right lower quadrant tender and painful?

DR. BLAND: As a matter of fact, in the Emergency Ward at first glance, it was thought by the house staff that she had a mesenteric embolus, but there was no real evidence pointing to that. Infarcts in the abdomen, in the kidney, and in the spleen would not give this picture. Infarcts of the kidney are usually painless unless there is a good deal of bleeding and clotting. Acute congestion of the liver is a complication that is sometimes confusing. She did not have that. In concluding, I am reasonably certain she does not have rheumatic fever now. The next time she has acute abdominal pain I think we should take her appendix out without delay.

DR. JONES: I will agree.

A PHYSICIAN: Would you comment on the presence of fever with acute pulmonary edema?

DR. BLAND: Dr. King put that question to us in January a year ago. This patient had a rectal temperature of 103°. We often see a degree or two from congestive failure alone. My comment at the time was that it seemed a little high for simple congestive failure. But this is not simple congestive failure. This is an acute widespread pulmonary congestion. In view of the fact that the temperature so promptly subsided, in fact the next day the temperature was down, I think we must assume that the acute pulmonary edema was the principal cause. Would you agree, Dr. King, or not?

DR. KING: I do not know. I was hoping someone would ask.

DR. WHITE: I think she must have had pneumonitis.

DR. BLAND: The sputum cleared quickly.

DR. GEORGE P. STURGIS: We had another case recently in the Boston Lying-in Hospital similar to this one. Pregnancy was interrupted by therapeutic abortion. Six days later she had a chill and fever. Twenty minutes later she went into acute pulmonary congestion. We thought probably the precipitating mechanism was the tachycardia connected with the chill. She became very apprehensive when she had the chill, although she was apprehensive anyway. She presented very much this picture before oxygen was given.

She now has evidence of acute rheumatic fever with prolonged P-R interval.

DR. BLAND: You probably thought she had an infection too.

DR. STURGIS: It was never proved.

DR. CONGER WILLIAMS: Don't you think the cases which develop considerable temperature should be designated by a special term? We have had five patients who have had just this thing, characterized first by the high temperature, with pulmonary edema, in which they have been diagnosed almost invariably as pneumonia. Dr. Soma Weiss about five years ago reported a similar group of cases which he termed pulmonary apoplexy.

DR. WHITE: Did this patient have a calcified mitral ring?

DR. ROBBINS: I think you can see something. I do not think it is mitral valve that you see. The annulus is probably calcified. The original interpretation here said, "No calcification was seen," meaning it was thought there was some, but that it was not certain from the fluoroscopist's observation.

DR. BLAND: Yesterday we were sure this patient

should have had a calcified mitral valve. I searched assiduously for a calcified mitral valve and we agree that she has one.

DR. ROBBINS: How do you differentiate the valve from the annulus?

DR. BLAND: The calcification is in the region.

DR. ROBBINS: I think the annulus may be seen in the film.

DR. BLAND: We think there is calcium in the neighborhood of the mitral valve, at any rate.

### *Editor's Follow-up Note*

This patient was seen in the Rheumatic Fever Clinic on the 10th and 24th of April, 1947, on the last of which visits it was decided, because of malaise, anorexia, and slight increase in dyspnea, that she probably had active rheumatic fever and that she should remain at home in bed for some time. She was seen in the Surgical Outpatient Department on the 14th of April, at which time it was decided to postpone operation until such time as an acute episode of appendicitis should recur.

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## WHAT'S YOUR DIAGNOSIS?

A 65-year-old white man was admitted for the second time on May 16, 1940, and died on the same date.

### FIRST ADMISSION

The first admission was on February 29, 1940, for investigation of precordial pain and shortness of breath. For one year he had attacks of knife-like or needle-like pain which began in the precordium and radiated to the left shoulder and down the left arm as far as the wrists. The precordial pain lasted for only a few seconds but the pain in the arm often persisted for 10 or 15 minutes. Pain in forearm and wrist often occurred without pain in the chest. The pain seemed to be unrelated to exertion, posture or food. It seemed to be aggravated by worry and nervousness. It was never associated with nausea, dyspnea or fear of death.

He had been mildly dyspneic and for eight months had ankle edema which subsided at night. These symptoms had increased during the week before admission when he had an upper respiratory infection. Orthopnea had been worse during this period.

He also gave a history of midepigastria pain, flatulence and intolerance to a variety of foods. The pain usually came on after food. A gastro-intestinal series taken nine months before was said to reveal "stomach ulcers." He had been treated with a soft diet and aluminum hydroxide. Nocturia two to three times nightly with mild oliguria had been present for two months. Twenty years before he had had jaundice associated with fever of about two weeks' duration. Twenty-five years before admission he had been rejected on an insurance examination because of a heart murmur.

Physical examination revealed a pale, elderly, slightly orthopneic man who did not seem to be entirely clear mentally. Pupils reacted normally to light. The retinal arteries were thickened and tortuous. No scars or hemorrhages were seen in the fundi. Thyroid gland was not enlarged. Expansion of the chest was poor but equal bilaterally. There was dullness at both lung bases with suppressed breath sounds. There were patchy areas of increased breath sounds with numerous crackling râles there as well as in the bases.

The heart was markedly enlarged. The supra-cardiac dullness was increased to the left. The right border was 5 cm. and the left cardiac border was at the anterior axillary line. Heart was rapid with numerous extrasystoles. The sounds at the apex were diminished. The aortic sound was increased with a tambour quality.  $P_2$  in the third interspace on the left was increased and split. A systolic murmur of about grade 2 intensity was present over the base. An inconstant gallop rhythm was heard at the apex. There was a distinct pulsation in the second and third left interspace about 4 to 6 cm. to the left of the sternum. The peripheral arteries were markedly thickened and tortuous with some beading. Blood pressure was 180/140 in the right arm. A paradoxical pulse was discernible over a range of about 15 mm.

The abdomen was full with some right upper quadrant resistance and tenderness. The liver edge was smooth, firm, slightly tender and extended four fingersbreadth below the costal margin. No other masses or organs were palpable.

The remainder of the examination was not remarkable except for slight pitting edema of the ankles. The reflexes were normally present and equal.

## LABORATORY DATA

Electrocardiogram (Feb. 29): PR 0.20, rate 88, ST<sub>1</sub> elevated, arborization block, premature ventricular contractions. (March 6): Essentially as before except ST<sub>1</sub> was less elevated. PR 0.22.

Urine	FEB. 29	MARCH 1	MARCH 5
Sp. Gr.	1.034	1.030	1.025
Albumin	2 +	2 +	1 +
Sugar	0	0	+
Micro.	WBC 1/hpf. No RBC, few casts		

Blood	FEB. 29	MARCH 1	MARCH 2	MARCH 5
RBC	5,011,000			
WBC	6,250		7,750	4,650
Hgb	12.6 Gm.			
Sed. Rate	2			
PCV	39			
Kahn	Neg.			
NPN	35			41
Blood Sugar	148			80
Icterus Index		15		
Uric Acid		3.6		
Cholesterol		192		

Stool (March 2): No blood or parasites.

PSP (March 2): 70 per cent in two hours.

Course: The patient was digitalized, weight fell from 132 to 121 lb. in six days. He was discharged on March 6 to be maintained on digitalis. He had improved considerably while in the hospital.

## SECOND ADMISSION

He was readmitted on May 16, 1940, in a semicomatose state and with dyspnea. History was obtained from the patient's wife. He had continued to have attacks of precordial pain as well as pain in the left shoulder, pain in the back and abdomen. One month before this admission he had a severe attack of pain in the chest and abdomen that persisted for 12 hours and required morphine for relief. The pain was not relieved by nitroglycerin. Five days prior to admission he developed increasing dyspnea, edema and oliguria. He continued to take 0.1 Gm. digitalis daily. The day before admission he was given salyrgan despite the fact that he had not voided for 16 hours. He was given some medicine to make him sleep and could not be aroused on the day of admission.

Physical examination revealed a semicomatose man who appeared acutely ill. He was moderately dyspneic and a urinous odor was discernible on his breath. Fundi revealed arteriosclerotic changes. Pupils reacted sluggishly. There was marked venous distension of the neck. There was dullness with diminished breath sounds at the bases which was most marked on the right. Very few râles were heard at the bases. The heart was enlarged to 3 cm. outside the midclavicular line on the left and 1 cm. outside the right sternal border. A loud blowing systolic high pitched murmur in the pulmonic and aortic areas was described. A loud blowing systolic murmur was also heard at the mitral area.  $A_2 = P_2$ . No gallop, friction rub, thrill or shocks were observed. Blood pressure was 100/20 in the right arm and 105/50 in the left.

The abdomen was completely rigid but not distended. Left rectus muscle was a little more rigid than the right. Liver was percussed as down three fingersbreadth. A systolic blow was heard in the epigastrium. No fluid was present. Reflexes were normal. Physical examination was otherwise unchanged.

## LABORATORY DATA

Electrocardiogram (May 16): Rate 107. No regularly spaced P waves. T<sub>2,3</sub> inverted. ST<sub>1</sub> elevated. R<sub>1</sub> absent. Nodal rhythm with A-V block was thought to be present. Urine (May 16): Albumin 3 +, otherwise negative.

Blood (May 16):

RBC: 3,870,000.

WBC: 11,700.

Differential: Segmented 87, lymphocytes 11, monocytes 2.

NPN: 120.

Course: The patient died in circulatory collapse 5 hours after admission.

# Clinicopathologic Conference

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## CASE HISTORY

Duke Hospital History No. B 59122

A 36-year-old white married female, para 4-0-4, was admitted to Duke Hospital on August 6, 1945, for evaluation of hypertension that had been present for six years.

**Present Illness.** The onset of her illness was characterized by vertigo, by which she meant a sense of fullness in her head and severe frontal and occipital headaches which were present only upon awakening in the morning. The onset of her headaches was quite sudden, and six weeks after she noticed them she consulted her physician, who informed her that her blood pressure was high. She had no other symptoms at that time and no therapy was instituted except for some medication, the nature of which is not known. No remarkable symptoms were noted other than the vertigo and headaches until two and one-half years before admission to the hospital. At that time the headaches and vertigo increased, and for the first time she noticed palpitation, slight exertional dyspnea, and ankle edema. At about this time the patient noticed the onset of "drawing spells," which would come on at varying intervals. She was admitted to a hospital for two weeks, where studies were carried out, and she was placed on a diet consisting of dairy products, rice, toast, and vegetables without salt. Some improvement was noted. However, her symptoms recurred, and a note is made in the record that "her course has been one of partial, temporary improvement and then a recurrence of her symptoms." She was unable to work and spent the greater part of her time in bed, particularly after having the attacks which will be described. In response to the question, "Do you ever feel your heart pounding?" the patient replied, "Yes, and it comes in attacks. I have these

attacks when my blood gets high. It doesn't last very long, only a few minutes. When I have one of these spells I am more irritable. By spells I mean that something goes all over me and I draw backward and can't speak for a moment. However, I do know what is going on. My neck goes backwards, but I never drop to the floor." There has been a gradual progression in severity of the attacks and the frequency. At all times her blood pressure was found to be quite high. Nine weeks before admission the patient noticed scotomata, which had not been present previously.

**Past History.** The past history reveals that two and one-half years before admission the patient had a period of time during which she had frequency, urgency nocturia, dysuria, and in 1938 she had severe abdominal and flank pain radiating to the groin. This was not followed by hematuria or any evidence of passage of stones. Her menstrual history was entirely normal.

**Physical Examination.** The temperature was 37° C., and the pulse was 80. Blood pressure was 210/130. The weight was 116 pounds. The patient was a well developed, slightly underweight white woman who was in no distress. The skin was normal. There was normal distribution of hair. The veins of the oculi fundi showed slight arteriovenous compression. The disks were sharply outlined. No hemorrhages or exudates could be seen. There was no enlargement of the thyroid. The breasts were of normal development with no masses or tenderness. The lungs were clear. The heart was not enlarged; A<sub>2</sub> was accentuated. No murmurs were heard. The abdomen was soft; there was no tenderness. The liver and spleen were not felt. One observer felt a mass in the left flank, which he thought to be the size and shape of the kidney pole. This observation was not confirmed by others. The pelvic and rectal examinations were

normal. The neurologic examinations were normal.

Urologic consultation was obtained and no contra-indication was found for a proposed total sympathectomy. This was also the impression of the psychiatric consultant.

**Accessory Clinical Findings.** The hemoglobin was 91 per cent; WBC 12,100. The serum Kahn and Kline reactions were negative. The blood NPN was 32 mg./100 cc.; urea nitrogen 10.1 mg./100 cc., and urea ratio of 31.6. Mosenthal concentration test showed the urine to vary in specific gravity between 1.003 and 1.018. PSP excretion test showed an appearance time of five minutes, and in the first half hour 43 per cent was excreted, a total of 59 per cent for the entire test. The x-ray of the chest was normal. A flat plate of the abdomen was normal. Intravenous pyelograms showed delayed excretion and possibly some dilatation in the pelves. There was a mass in the bladder region, "probably a large uterus." The EKG is reported as follows: "Rate 75, P-R interval 0.16 sec. QRS interval 0.06 sec. Normal sinus rhythm. No axis deviation. Low upright  $T_1$ . Upright  $T_2$  and  $T_3$ . Inverted  $T_4$ . Diagnosis: Normal sinus rhythm. Conclusion: Record abnormal due to change in  $T_1$  and  $T_4$ ." Routine examination of the urine was normal. Sodium amytal test showed no appreciable fall in the blood pressure, and a cold pressure test showed only a slight rise in the blood pressure. While in the hospital, before operation, the systolic blood pressure varied between 170 and 200, while the diastolic pressure remained at about 120 mm. Hg.

**Course in Hospital.** After the patient had been studied for one week she was prepared for operation (sympathectomy) in the usual manner and was given morphine, 10 mg., and atropine, 0.4 mg. Ethylene and ether anesthesia was used, and a note is made on the anesthesia chart that the patient was very apprehensive before the anesthesia was started. The operation was begun with the skin incision made in the usual fashion, and at this time the blood pressure became imperceptible. It is to be noted that the blood pressure at the start of the operation was 190/100 and after ten minutes had risen to 240/160. This pressure was persistent for some ten to fifteen minutes, and then it was unobtainable by the anesthetist. The operation was stopped immediately and supportive measures in the form of neosynephrin and oxygen were given. When the patient returned to the operating room, the blood pressure had fallen to 110/90. She was then given 500 cc. of blood, which failed to bring about any response. The evening of the operation the blood pressure had risen to 150/120 with a rapid,

weak pulse of 160. She was described as being cold, clammy; and in "peripheral collapse." There were râles over both lung fields, and the heart was enlarged. She was digitalized with Ouabaine. Her temperature had now risen to 39.7° C. Three EKG tracings were made during the last 24 hours of life, and these were reported as follows: No. 1.—"Rate 160, Diagnosis: Sino-auricular tachycardia. Conclusion: Since previous record  $ST_1$  is depressed and flat.  $ST_2$  shows minimal elevation.  $RST_3$  shows definite elevation of 1 mm.  $T_4$  diphasic. ST segment changes are suggestive of possible early posterior infarction. No. 2.—Rate 165. Diagnosis: Sino-auricular tachycardia. Conclusion: Since previous record there is further inversion of  $T_1$ . Flat  $T_2$  with elevation of RST segment and further elevation of  $RST_3$ .  $T_4$  is now inverted. No. 3.—Rate 175.  $QRS_1$  is now notched with a high origin of RST segment and late inversion.  $RST_2$  and  $RST_3$  show remarkable high elevation with beginning inversion of  $T_2$ .  $RST_4$  likewise shows elevation. RST segment changes would suggest either a pericarditis, since it involves all three leads, or else combined anterior and posterior infarction."

In spite of all supportive measures the patient died some 24 hours after the start of the operation. The blood pressure had fallen to the quite low level of 68/58 shortly before her death.

A lumbar puncture was done with the removal of a clear fluid which contained no cells. Spinal fluid protein on this was 58 mg./100 cc.

## CLINICAL DISCUSSION

DR. NICHOLSON

There are certain features of this patient's history that will allow a discussion of one of the etiologic agents in the production of hypertension. I would like to divide the discussion into two parts: (1) the etiology of the hypertension, and (2) the events that led to the collapse and death of the patient.

As to the etiology of the hypertension, certain factors are to be weighed; and, although no definite conclusions can be reached from the information that is available, at least certain suggestions are apparent. First of all, there is little evidence to support the idea that the hypertension was on the basis of a renal lesion. There was some reduction in the function of the kidneys, as evidenced by impairment of the efficiency of the PSP excretion test, the failure to concentrate the urine during the Mosenthal test and the history of a short transitory urinary tract infection in 1938. At the time of admission the urine was normal. There was no nitrogen retention, and therefore it

would be most unlikely that this patient had nephritis or chronic pyelonephritis.

Essential hypertension cannot be unequivocally eliminated from the list of possibilities. Indeed, with the information available, this diagnosis would seem more likely. However, when the parts of the pattern are placed together, a definite picture begins to manifest itself which does not resemble precisely that of patients with essential hypertension.

For the sake of this discussion we will assume, therefore, that this patient had neither parenchymatous disease of the kidneys nor essential hypertension. One other group of etiologic factors, the hypertension associated with disturbances of the endocrine system, must be considered in patients with hypertension, particularly in the age group represented by this case. These may be: Cushing's syndrome (basophilism of the anterior hypophysis, tumors of the adrenal cortex, or tumors of the thymus gland), arrhenoblastoma, and pheochromocytoma. It would seem to me that, except for the adrenal medulla, the endocrine system can be excluded from our discussion. This patient had none of the symptoms or signs associated with thyrotoxicosis. Except for the hypertension, the same may be said of Cushing's syndrome or arrhenoblastoma. Therefore we must look to the adrenal medulla for an explanation of the events that led to this patient's death. Actually such a tumor need not be located in the adrenal medulla, but may be situated in any of the chromaffin tissues of the body (paraganglioma).

The paroxysmal nature of the symptoms that are produced by a pheochromocytoma is well known. The flushing of the skin, particularly of the face, throbbing headaches, palpitation, substernal oppression, sweating, apprehension, and other symptoms of sympathetic stimulation have been reported frequently in patients who have such a tumor.<sup>1</sup> Why should these symptoms occur only upon occasion, while in the interim the patients are normal? Patients have been reported in whom the paroxysm was produced by palpation of the abdomen. Therefore it is assumed that the paroxysms are produced by increased pressure or other stimulus upon the tumor, allowing a release of excessively large amounts of adrenalin. That this mechanical stimulation of a mass located in some of the endocrine glands takes place is supported by a patient seen in this clinic with an adenoma of the parathyroid gland. Following frequent palpation of the neck the serum calcium of the patient rose to over 22 mg./100 cc., and this was followed by death of the patient. Since it is known that a release of adrenalin will produce the paroxysmal attacks that are described above, can it not be

that a point is reached in the evolution of the disease when there is a constant oversupply of adrenalin to the organism? There is no history of repeated blood pressure determinations in this case, but only a record of hypertension for six years. The actual observations were made after the patient was admitted to the hospital; then it was found that the blood pressure recordings were always over 200 systolic and 100 diastolic. So it may have been that during the first part of her illness the blood pressure was normal except for the periods during which the headaches became much worse. At some time the disease became more severe, more adrenalin was being released, and for some reason the supply of adrenalin was at a higher level than it had been previously; the blood pressure then became persistently elevated. Assuming that the patient did have an additional supply of adrenalin, the attacks that she had were undoubtedly on the basis of an even greater release of adrenalin. There are other conditions that must be considered to explain the attacks that she had: idiopathic epilepsy, hypoglycemia, and hypertensive encephalopathy. However, the pattern is not the typical history of those conditions. There are no laboratory studies made that would aid one in arriving at any definite conclusion in regard to these attacks.

Since the patient did have a persistent hypertension, there is ample evidence to support the view that a medullary tumor may produce this phenomenon. Thorn, Hindle, and Sandmeyer<sup>2</sup> and others have reported such cases.

The second part of the discussion concerns itself with the vascular collapse that preceded death. Assuming that a tumor of the adrenal medulla was present, the manipulation of the patient in preparation for a transthoracic sympathectomy may have produced an even greater release of adrenalin into the circulation. Under those circumstances the events as recorded could be explained. The events, as I picture them, are as follows: release of excessive adrenalin, arterial constriction, capillary dilatation, followed by shock.

Since the patient had hypertension for several years, it is assumed that some damage to the myocardium had taken place. This fact is substantiated by the changes in the electrocardiograph. Since more adrenalin was released, more work was forced upon the heart, with resulting coronary insufficiency, which was followed by myocardial infarction. It is not necessary to suppose that occlusion of a coronary artery had occurred. In fact, one would suppose that this was not the case.

There is evidence to support part of this view, and

that is the electrocardiographic tracings, which showed marked changes during the last 24 hours of the patient's life.

**Diagnosis.** Hypertension due to pheochromocytoma or paraganglioma. Death due to release of adrenalin with increased work of heart, coronary insufficiency, and myocardial infarction.

## PATHOLOGIC ANATOMY

DR. MARZONI

In this case there are three lesions that are of great importance. The first of these is a tumor in the left adrenal gland, measuring  $8 \times 5 \times 3$  cm. This tumor is a fleshy mass, well circumscribed though not encapsulated. The tumor is of a brownish color with a good deal of translucency. There are no cysts, and the tumor does not appear to be extremely vascular. The tissue of the tumor resembles medullary rather than cortical tissue, and it is surrounded by a thin, compressed layer of adrenal cortex. The second lesion of importance is a fresh thrombus on the wall of the left ventricle of a dilated heart of normal weight, 320 Gm. The cause of the thrombosis is difficult to determine, but it appears grossly that the interventricular septum is involved in an infarct. The third important lesion is a large hemorrhagic infarct in the right hemisphere of the cerebrum involving an area corresponding to the distribution of the right middle cerebral artery. The infarct measures 6 cm. in greatest diameter. The normal pattern of cortical tissue is still recognizable, but there is much hemorrhage within the softened area of necrotic brain substance. No thrombus can be found in the middle cerebral artery on gross examination. Both lungs show edema and some atelectasis. Another lesion of interest, one which probably contributes little to the understanding of the case, is in the thyroid gland. This gland is considerably reduced in size and contains relatively little colloid. The entire gland is extremely scarred. Attached to the fundus of the uterus is a pedunculated fibromyoma 6 cm. in greatest diameter. The left ovary contains an active corpus luteum.

As determined by microscopic examination, the tumor in this case is a typical pheochromocytoma composed of large cells filled with brown argentaffine (chromophil) granules, resembling normal adrenal medullary cells. These cells show considerably anaplastic morphologic variation, but little to indicate genuine malignancy. An interesting and important histologic feature of the tumor is extensive necrosis which has followed thrombosis or embolism of many of the vessels lying within the center of the gland.

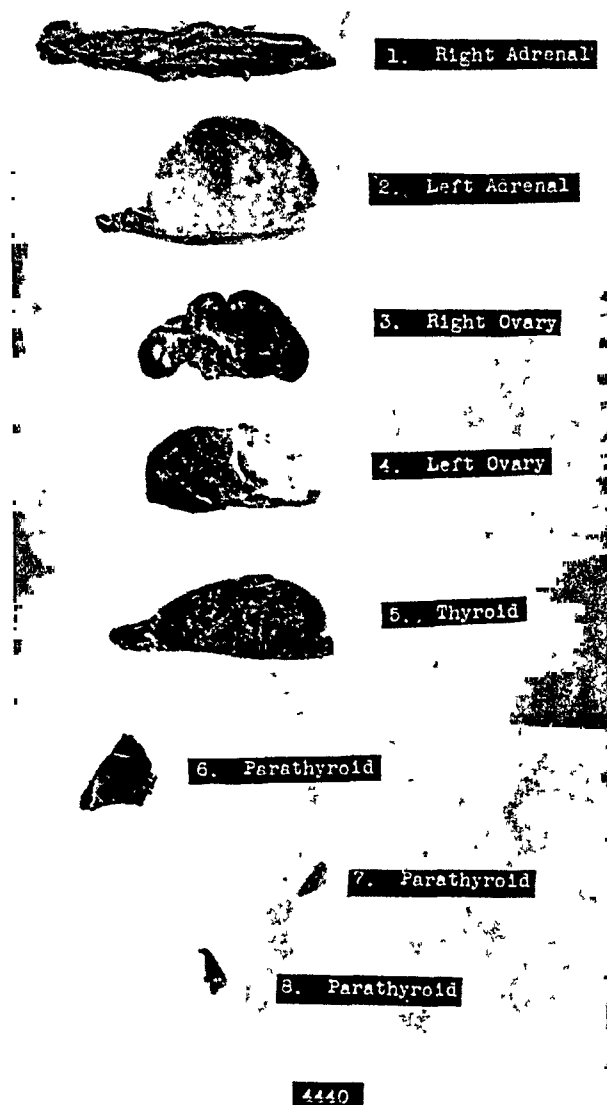


FIG. 1. Photograph of the various glands of internal secretion including the left adrenal with the pheochromocytoma. All the glands appear normal except the adrenal and the thyroid. The latter is greatly reduced in size due to extensive alterations, as described in the text. The ovary shows a fresh, active corpus luteum.

This is shown in the accompanying photograph. The microscopic preparations of the heart reveal a moderate amount of necrosis in the myocardium. This is focal in distribution and is most prominent in the interventricular septum. It is accompanied by emboli in many of the corresponding coronary arterioles. No large branch of the coronary arteries is obstructed, and there is no genuine infarction of the myocardium. Chronic passive congestion is pronounced in the liver, spleen, and kidney. Focal necroses are present in the liver. Sections of the hemorrhagic cerebral infarct show extensive embolism of the subarachnoid and intracerebral arteries and thrombosis of the correspond-



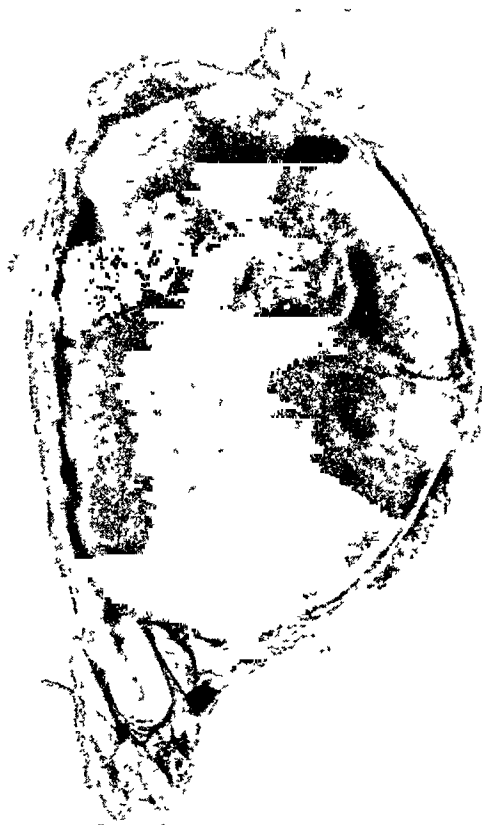


FIG. 2. The left adrenal containing the pheochromocytoma. Note the extensive necrosis and hemorrhage within the tumor and also its sharp gross encapsulation, indicating its benign character.

ing subarachnoid veins. The brain tissue itself is hemorrhagic and quite necrotic throughout. In the kidney there is dilatation of all capillaries, especially those of the glomeruli. Accompanying this may be seen either hyaline thrombi or capillary emboli. There is little arteriosclerosis. The thyroid gland shows extensive scarring, replacement of the acinar tissue by lymphoid tissue, great irregularity and degenerative and regenerative disorganization of the persisting thyroid epithelium, and little colloid. The histologic picture is that of the characteristic Hashimoto struma.

## GENERAL PATHOLOGIC INTERPRETATION

DR. FORBUS

A satisfactory interpretation of this case requires the following procedures:

1. An evaluation of the clinical diagnostic procedures and the conclusions based upon them.
2. Critical judgment of the various anatomical findings, especially with respect to their relationship



FIG. 3. Coronal section of the brain illustrating the large hemorrhagic cerebral infarct. The thrombosed vessels responsible for this lesion are not visible.

to each other and to the pathogenesis of each of them.

3. Detailed correlation of the functional disturbances observed during the course of the patient's illness, especially those occurring during the terminal stages of the disease, and the anatomical lesions found at autopsy.
4. An integration of all of the data assembled during the course of the disease in such a way that a sharply defined clinico-pathologic entity may emerge if such an entity exists.

**Evaluation of the Clinical Procedures and Opinions.** The clinical data, as recorded, are quite adequate for an accurate analysis of the problems which the case presents. The patient was under observation long enough, both preceding entry to the hospital and thereafter, for accomplishing the procedures essential to diagnosis of the disease. Nevertheless, careful review of the history and the clinical studies reveals the absence of certain data which, though not essential to a gross diagnosis, would have contributed significantly to the development of a more complete story of the disease entity which this patient presented. The data referred to relate especially to the blood pressure during the years preceding entry of the patient to the hospital. We do not have specific knowledge of the relationship of the blood pressure measurements to the acute attacks which the patient suffered. Presumably the blood pressure determinations were made only at intervals, and we therefore do not know

whether the elevation of blood pressure during the early stages of the disease was sustained or paroxysmal. Frequent observations of blood pressure during the patient's hospitalization show that there was sustained, though variable, elevation; but this does not permit the assumption that the blood pressure was always of this character.

Although deprived of a detailed record of the blood pressure determinations during the early phase of this patient's disease, Dr. Nicholson recognized at once that the major problem presented was that of hypertension. He was therefore amply justified in devoting his attentions first to the problem of determining the basic character and origin of the elevation of blood pressure. His successful elimination of primary renal disease and that as yet unknown factor which produces the typical essential or primary hypertension as possible causes of the hypertension requires no comment other than to say that the data essential for this were present, and they were skilfully handled. The same comment may be made on the clinical differentiation between the various forms of endocrine hypertension, although data available for this differentiation were neither so abundant nor so definitive.

The decision to assign the hypertension in this case to medullary hyperadrenalism appears to have been based upon both negative and positive data. The negative data consist chiefly of the absence of any other possible explanations of the hypertension, and the positive data of the fact that the signs and symptoms were those peculiar to a stimulation of the sympathetic nervous system, namely, flushing of the skin, palpitation of the heart, throbbing headache, substernal oppression, sweating, apprehension, and hypertension. The fact that the hypertension was, as far as the record shows, a sustained one quite rightly did not block this decision because experience with cases of medullary hyperadrenalism has taught that, whereas the hypertension is characteristically paroxysmal, sustained blood pressure is not uncommon, especially during the terminal phase of the disease.

Being without a careful record of the blood pressure preceding admission of the patient to the hospital, Dr. Nicholson has been cautious and has entertained the idea that the peculiar attacks which the patient suffered may have been related to other disease processes than hypertension, for example, epilepsy and hypoglycemia, and even that little-understood clinical complex, hypertensive encephalopathy. The elimination of these possible explanations of the patient's attacks seems to have been accomplished successfully.

It is thus evident that the clinical analysis of this case up to the onset of the terminal event is character-

ized by accuracy and completeness. From this point on the available data, though comprehensive, do not permit an accurate estimation of what actually took place. The clinical diagnosis of a terminal vascular collapse due to "adrenalin shock," though quite correct, is nevertheless a very gross estimate of the situation. To have accomplished more than this, as is usually the case, required more time than the rapid progress of the disease allowed. Attempts at detailed specification of the events occurring during the terminal phase of this complicated disease process usually amount to little more than good guessing based upon experience with similar cases. Dr. Nicholson's guessing in this case was remarkably good, with the exception of one fundamental and highly important detail. He has summed up the final course of events as follows:

- a. Arterial constriction due to release of adrenalin from the adrenal medullary tumor.
- b. Elevation of blood pressure.
- c. Capillary injury and dilatation.
- d. Shock—fall in blood pressure.
- e. Coronary insufficiency.
- f. Myocardial infarction.
- g. Myocardial failure with general circulatory failure followed by death.

The error in this, as may be seen from Dr. Marzoni's description of the pathologic anatomy of the case, lies in the failure to recognize what took place in the heart.

#### Nature and Pathogenesis of the Anatomic Lesions

1. THE ADRENAL TUMOR—PHEOCHROMOCYTOMA. The tumor arose from the medulla, and the cells composing it are chromaffin in nature, just as are the medullary cells of the normal adrenal. The tumor is thus of sympathetic nervous system origin, but it is composed of cells which are highly differentiated—so much so, in fact, that they are capable of producing adrenalin, the normal product of the adrenal medulla. The size of the tumor is within the described limits. The adrenalin content of this tumor was not determined. In cases similar to this one the larger tumors have been assayed and have been shown to contain as much as 2,300 mg. of adrenalin. This quantity is in striking contrast to the 1 to 8 mg. found in the normal adrenal. The tumor is highly vascular, and the cells lie immediately adjacent to capillaries of wide caliber, thus facilitating the entry of their products directly into the blood. Necrotic areas related, as a rule, to capillary obstructions produced by hyaline thrombi, or perhaps small emboli, are numerous. Evidences of

malignancy are lacking. Some neoplasms which produce the clinical syndrome illustrated by this case are malignant and give rise to widespread metastases. Pheochromocytoma is readily differentiated from other tumors arising from the sympathetic tissues of the adrenal gland which have no endocrine properties. These are the gangliomas, ganglioneuromas, and sympathoblastomas. The latter is the most common of all the adrenal tumors and is one of the most highly malignant neoplasms of man. The gangliomas and ganglioneuromas are rare tumors, but not so rare as the pheochromocytomas. As with all neoplasms, the causation of the neoplastic process in this case is not understood.

2. **THE CAPILLARY INJURY AND DILATATION.** The nature of the capillary lesion is not understood. Presumably the adrenalin injures the capillary endothelium and perhaps also the cells which control the size of the capillary lumen, the rouget cells; thus may be brought about the dilatation of these vessels that is so characteristic of adrenalin shock. Slowing of the capillary circulation which accompanies the dilatation is an important factor in the development of capillary thrombi. Obstructive capillary lesions are found in this case in virtually all of the tissues, especially the kidneys, the brain, and the heart muscle.

3. **FOCAL NECROSIS OF THE MYOCARDIUM.** Contrary to the clinical prediction, there was no myocardial infarction, nor was there obstruction of any of the larger branches of the coronary arteries. However, there was extensive focal necrosis. This is the natural consequence of injury to the capillaries, an adrenalin effect, and embolism of the capillaries and some of the smaller arterioles by thrombi originating in the left ventricular mural thrombus. The capillary embolism appears to have been a late occurrence.

4. **MYOCARDIAL DILATATION.** Dilatation of the heart came late; it seems to have occurred after the patient returned to her room following the operative episode. This dilatation unquestionably was the result of coronary vascular insufficiency with its resulting myocardial focal necrosis.

5. **LEFT VENTRICULAR MURAL THROMBOSIS.** This lesion, as usual, was the result of myocardial injury, myocardial dilatation following that injury, and the consequent slowing of the movement of blood through the heart. Stagnation of blood was further complicated by the relative insufficiency of the valves which followed the initial ventricular dilatation.

6. **ARTERIAL EMBOLISM.** The source of the widely disseminated small arterial emboli was the thrombus on the wall of the left ventricle. These emboli are conspicuous in the brain and the myocardium. The

embolic process was late in development, but it occurred sufficiently in advance of death to allow the formation of typical infarcts, as noted below.

7. **CEREBRAL INFARCTION.** This lesion developed late and was the result of two processes, cerebral arterial embolism and cerebral venous thrombosis. The development of infarction was favored significantly by pre-existing capillary stasis and thrombosis.

8. **FOCAL MYOCARDIAL NECROSIS FROM CORONARY EMBOLISM.** As previously noted, the coronary emboli originated in the mural thrombus of the left ventricle. Lodgement of these emboli in the branches of the coronary arteries and capillaries accentuated the coronary insufficiency which followed the initial circulatory collapse of the patient during operation.

9. **FOCAL NECROSIS OF THE LIVER.** It is difficult to explain this lesion. It may be suggested that capillary thrombosis doubtless occurred in the liver, as it did elsewhere. This, in combination with hepatic arterial embolism, is the best explanation of the lesion that can be offered.

10. **CHRONIC PASSIVE CONGESTION AND PULMONARY EDEMA.** Both of these lesions were the consequence of myocardial failure followed by a general circulatory disturbance.

11. **PULMONARY ATELECTASIS.** In pulmonary edema and chronic passive congestion of the lung the bronchi often become filled with fluid which includes a considerable proportion of mucus. This material obstructs the smaller bronchi and sometimes the larger ones, and the result is atelectasis. This seems to have occurred in our case.

12. **FIBROMYOMA OF THE UTERUS.** This lesion is unrelated to any of the other lesions in the case and is of no functional significance. It is an incidental finding. Since the lesion is a pedunculated mass which could have lain above the rim of the pelvis, it may have been felt by the clinical observer who reported that he had noted a tumor mass in the region of the left adrenal; but this observation was not confirmed. It now seems likely that the observation of a mass in the region of the adrenal was correct, but whether the mass was the adrenal tumor found at autopsy or the uterine myoma is still doubtful.

13. **HASHIMOTO'S STRUMA.** This is a relatively rare lesion of the thyroid gland of peculiar type. Hyperthyroidism is not usually produced by the lesion. Its finding in this case is incidental. It is unrelated to any of the other pathologic processes.

14. **EARLY ACTIVE CORPUS LUTEUM.** Although one cannot attribute any significance to the presence of an active corpus luteum in this case, it is worth remembering that the stage of the menstrual cycle corre-

sponding to an active corpus luteum is characterized by widespread vascular instability. That this may have favored the development of adrenalin shock is an intriguing possibility.

### Clinicopathologic Correlation

Viewing this case in retrospect, it seems possible to correlate rather accurately the various anatomic and physiologic states which stand out prominently in the development of the disease. The state of the patient at six successive points in the course of the disease may be profitably discussed.

1. **THE ONSET OF THE DISEASE.** The disease began six years previous to death. It was characterized at that time by vertigo, morning headache, and what proved in subsequent examinations to be an elevation of blood pressure. From what we know of the development of pheochromocytoma, it can be said that the tumor must have been present at that time, but that its endocrine activity was limited, reactions to the products of the tumor having been produced characteristically following exertion incident to physical activity after a period of rest. It may be assumed that the growth of the tumor progressed from onset of the disease to the next period to be considered, since the signs and symptoms became more severe and the attacks more frequent in occurrence. The record does not give us sufficient information regarding this period to make possible a more detailed correlation.

2. **THE SITUATION 21½ YEARS BEFORE DEATH.** At this time the history records recurring attacks of headache, vertigo, palpitation, dyspnea, ankle edema, and "drawing spells." It is noted that these attacks became increasingly frequent, the intervals between them becoming progressively shorter as time elapsed. The blood pressure was always high when recorded, but we have no series of recordings that tell us what the blood pressure was between the attacks. The functional disturbances of this period indicate clearly an increase in the size of the tumor and a corresponding increase in adrenalin production. It may be assumed that the attacks were brought on by periodic release from the tumor of relatively large quantities of adrenalin incident to normal or special demands for this product.

3. **STATUS OF THE DISEASE NINE WEEKS BEFORE DEATH.** At this point a new element enters the case. Scotomata were observed along with what was thought to be a sustained elevation of the blood pressure. Severe attacks recurred at intervals, but the patient apparently was continuously ill. The development of the visual disturbances correlates well with the onset of significant vascular, that is, capillary, injury and

dilatation, perhaps with thrombosis. It is not surprising that these lesions developed within the retina.

4. **STATUS OF THE DISEASE ON ADMISSION ONE WEEK BEFORE DEATH.** Observations at this time revealed a sustained high blood pressure ranging around 200/100. Other signs of sympathetic stimulation were prominent. At this time a tumor mass was felt by a single observer in the left upper quadrant in the kidney region. This was not confirmed. In spite of the sustained high blood pressure, the heart was not enlarged. This lack of correlation indicates that the sustained blood pressure must have been of short duration; certainly it had not been present six years. The sustained blood pressure indicates, however, continuous secretion of adrenalin by the growing tumor, the quantity of this hormone in the blood always being maintained at an abnormally high level. At this point in the development of the disease it became apparent that the sustained high blood pressure could not be correlated with any of the common pathologic processes which are usually accompanied by hypertension, such as renal disease; but it was possible to correlate it with a pure sympathetic nervous system effect. Sympathectomy was therefore accepted as a promising form of therapy. The adrenal tumor had not been diagnosed, although in the pre-operative study of the case every consideration had been given to the possibility of the existence of such a tumor.

5. **THE OPERATIVE INCIDENT.** The patient was described as being in a severe state of anxiety just preceding administration of the anesthetic. This may be interpreted as the result of a rise in the adrenalin content of the blood. Shortly after the anesthetic was administered the patient developed a sudden rise in blood pressure; this was followed by a severe fall in the blood pressure and a state of shock. The manipulation of the patient necessary to preparation for the operation and the excitement produced by the anesthetic appear to be a satisfactory explanation of the sudden rise in pressure, in view of the well-known effects of such conditions upon the liberation of adrenalin from adrenalin-producing tumors. The collapse which followed the initial sudden rise of blood pressure is attributable to the development of a relative adrenalin insufficiency which is known to follow excessive excretion of adrenalin from tumors of this type. The gradual recovery of the blood pressure which occurred following the collapse can be correlated satisfactorily with a return of adrenalin secretion from the tumor and from the normal adrenal medulla to the level to which the patient had become adjusted.

6. **THE TERMINAL EVENTS.** Even though the patient's blood pressure returned to normal levels fol-

lowing return to her room, the circulatory collapse, especially that in the coronary system, never disappeared. Within a short time the heart dilated, and a succession of electrocardiographic studies clearly indicated serious injury to the myocardium. All of this correlates accurately with the development of focal myocardial necrosis—not infarction—with its natural sequellae, dilatation of the heart, mural thrombosis, and the onset of myocardial failure. The terminal events succeeded each other so rapidly that no clinical observations could be made which might be correlated with the cerebral arterial embolism and venous thrombosis and their consequence, cerebral infarction. As is so often true, death in this case may be considered the result of a combination of effects, namely, general circulatory failure and cerebral infarction. The basic pathologic process must be considered coronary circulatory failure, referable to vascular injury produced by hyperadrenalism, especially at the level of the capillaries.

#### Integration of All Data—Summary of Case

When all of the data, both clinical and anatomic, are assembled and properly correlated, the disease of which this patient suffered emerges as a distinct clinicopathologic entity, the nature and the course of which may be expressed in the following general pathologic diagnosis, the details of which are arranged in the order in which the various incidents most likely occurred:

Medullary hyperadrenalism following the development of a pheochromocytoma of the left adrenal and characterized by paroxysmal and sustained hypertension, convulsive seizures, vertigo, headaches, substernal oppression, palpitation of the heart, dyspnea, and ankle edema; generalized peripheral circulatory failure following release of excessive quantities of adrenalin into the circulation incident to anesthesia in preparation for operation; extensive focal myocardial necrosis following coronary circulatory collapse; dilatation of

the heart; mural thrombosis of the left ventricle; widespread arterial embolism, especially of the coronary and the cerebral vessels; thrombosis of the cortical cerebral veins; focal necrosis of the liver; hemorrhagic infarction of the right cerebral cortex; chronic passive congestion of the viscera; pulmonary edema; pulmonary atelectasis; Hashimoto's struma; pedunculated fibromyoma of the uterus; early corpus luteum.

#### CLOSING COMMENT BY DR. NICHOLSON

The difficulties of arriving at the diagnosis of a pheochromocytoma are many. The diagnosis will never be made unless one keeps it constantly in mind in dealing with patients with hypertension. Although one may make the diagnosis from the clinical evidence, it is frequently not confirmed at operation or at postmortem examination. Two patients come to mind immediately. One was a white male who had the characteristic paroxysmal attacks, with headaches, substernal oppression, sweating, elevation of the blood pressure and sugar. Upon exploration the adrenals and the chromaffin areas along the abdominal aorta revealed no tumor. Another patient, a young white woman, who had persistent elevation of her blood pressure showed by retrograde pyelograms depression of the left kidney. Perirenal insufflation revealed a rounded tumor mass above the left kidney, and upon operation a tumor was removed. Histologic examination of this tumor was not characteristic of a pheochromocytoma, and chemical analysis of the tumor failed to reveal adrenalin.

#### BIBLIOGRAPHY

1. Howard, J. E., and W. H. Barker: Paroxysmal hypertension and other clinical manifestations associated with benign chromaffin cell tumors (pheochromocytomata), *Bull. Johns Hopkins Hosp.*, 61:371, 1937.
2. Thorn, G. W., J. A. Hindle, and J. A. Sandmeyer: Pheochromocytoma of the adrenal associated with persistent hypertension, *Ann. Int. Med.*, 21:122, 1944.

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#### Answer to Quiz Case (Page 620)

Fusiform aneurysm of the ascending arch of the aorta, with two rents into the pulmonary artery.

# Migraine, 1947: A Review\*

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Migraine, known also as "sick headache," "liver headache," and "bilious headache," is estimated to occur in from 8 to 12 per cent of all patients seen in general practice. Women outnumber men by about four to one. It occurs quite frequently in "tense" individuals with more than average intelligence and drive. Onset is common during adolescence. However, no age or sex, social, intellectual, economic, or racial group is immune.

Migraine is a syndrome or symptom-complex, which though subject to considerable variation, is characterized by recurrent, often unilateral, headache occurring against a background of relative well-being. It is apt to occur in obsessive tensional personalities who often have an hereditary tendency toward migraine or the allergic states. It is usually preceded by visual disturbances, characteristically scotomata or hemianopsia. The headache is often associated with irritability, photophobia, blurred vision, nausea, vomiting, giddiness, flushing or paling. Perspiration, salivation, tics, tremors, paresis, paresthesiae, speech and mood disorders may also be present.

## ETIOLOGY

The etiology of this syndrome is unknown and may well be multiple. There is, however, a well recognized common mechanism responsible for the predominant symptoms. This is a cerebrovascular lability with (probably primary) vasoconstriction and (secondary) vasodilation, the latter producing the headache.

The basic pathologic processes in migraine are sources of considerable disagreement among students of the subject, but the final vasomotor mechanisms demonstrated by Wolff and his co-workers are generally accepted. These are as follows:

The preheadache scotomata have been shown to be due to vasoconstriction of branches of the internal carotid artery with resultant anoxia and distortion of occipital cortical function.<sup>1</sup> It is not unreasonable to assume that such symptoms as speech disorders,

paresthesiae, confusion, etc., are also the result of cerebrovascular constriction.

Repeated observations have shown that the headache is due to distention, chiefly, but not exclusively of the intracranial branches of the external carotid artery.<sup>1</sup> This dilation in turn may cause a rigid arterial wall refractive to vasoconstrictor drugs.<sup>2</sup> In addition, the underlying tension and the initial pain itself may cause sustained contraction of the cervical and scalp muscles with resultant cranial tenderness and pain.<sup>3</sup>

The pain itself is transmitted to consciousness by way of the fifth, ninth, and tenth cranial nerves and the upper three cervical nerves.<sup>4</sup> An intimate relationship is claimed between the migraine and Ménière's syndromes, if each be divided into primary vasodilator (histamine sensitive) and primary vasoconstrictor (histamine insensitive) types.<sup>5</sup>

The entire mechanism of vasomotor lability is intimately connected with underlying mood disorders, fundamental autonomic lability and perhaps allergic states.

All of the proposed basic causes of migraine are still to be regarded as distinctly theoretic. Among these may be mentioned: "toxic," colonic, duodenal, and hepatic disorders; various ocular malfunctions; thyroid, adrenal, and pituitary dysfunctions; "reflex headache"; cerebrospinal fluid alterations; cortical and nuclear discharges; and meningeal adhesions. The pituitary, hepatic, and toxic theories are most frequently mentioned, perhaps because of their deceptive simplicity. The pituitary theory entails the supposition that there is a temporary edema of the pituitary which causes the pain, and presumably all the other symptoms. There is no worthwhile evidence to substantiate this view. It has been shown that hepatic disease protects against, rather than produces migraine.<sup>6</sup> The theory that an accumulation of toxins causes the recurrent attacks is attractive in its simplicity. Although it is possible that these may occur during carbohydrate metabolism, substantiation awaits this demonstration.

There appears to be more evidence to substantiate

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the following conceptions although no one of these seems to be solely responsible for the various manifestations of migraine.

**Heredity** is agreed by all observers to play an important part in the production of migraine. There would also seem to be an hereditary relationship between migraine and epilepsy, possibly with the former predisposing to the latter. Commonly accepted allergic disorders also occur in from 30 to 40 per cent of the immediate relatives of patients with migraine. Emotional disorders are common in the ancestry of migraine sufferers.

**Personality.** The so-called "migraine personality" is another important etiologic factor. "Personality" may be defined as the algebraic sum of all endogenous and exogenous influences in a person's life (including hereditary tendencies), by reason of which the individual's attitudes and reactions assume a pattern which is specific for that person. Personality is not a rigid cast, but a continuously progressive fluid state, altering in character and degree according to the strength of previous influences and the impact of new experiences. In migraine it has been observed that the overwhelming majority of patients present common personality features which, though not pathognomonic of migraine, nor associated with migraine alone, are apt under certain conditions to call forth pernicious emotional reactions.<sup>7</sup> The predominant characteristics of this personality structure are: childhood shyness, obedience, neatness, reliability, and also stubborn inflexibility in certain circumstances; adult perfectionism, ambitiousness, inelasticity, tension, resentment, repetitiousness but also efficiency, poise, and social grace. As a result of this pattern the individual is in constant tension, with resultant autonomic and vasomotor lability. In such a setting vasomotor episodes such as migraine may occur frequently.

**Endocrinopathy** has been most seriously considered in the female because of the frequent association of migraine with puberty, the menstrual cycle, menopause, and the climacteric. It would seem, however, that the concept of gonadal etiology has been over-emphasized. Because of the biased point of view of many who have written on this subject and because of the varied therapeutic results, an analysis has been made of an unselected series of 65 males and 163 females with characteristic migraine.<sup>8</sup> In the male the syndrome more nearly approached the classical type. In the female the syndrome was definite but less characteristic. In only ten per cent was there a definite exclusive relationship between the migraine attacks and the menstrual cycle. Estrogenic therapy was most effective in this group and proportionately less effective

as this relationship became less definite. In 67 women who had one or more pregnancies 52 per cent were completely relieved during pregnancy. The autonomic and psychogenic aspects of puberty, the menses, menopause, and the climacteric seem to have been neglected in considering this aspect of migraine. Induction of the menopause for migraine by any means whatsoever is not recommended.<sup>9</sup> Endocrine therapy has, in general, been disappointing.

**Allergy.** An allergic etiology of migraine has been frequently proposed. Even those most enthusiastic in this respect admit, however, that there may be other contributing causes. In 862 cases of migraine reported by ten allergists, 661 cases were considered significantly allergic. In the 661, relief by allergic therapy ranged from 0 to 100 per cent with an average of 73 per cent. Complete relief was obtained by these means in only 25 per cent of the 862 cases.<sup>10</sup> In a few cases the etiology is unmistakably allergic.<sup>11</sup> Allergy warrants investigation in children with migraine or cyclic vomiting, and in patients of any age with a strong family or past history of allergy. The inhalants are relatively unimportant in migraine. Accurate food diaries and elimination diets are usually necessary to discover the responsible allergens.

No gross or histologic pathology, responsible organisms, or toxins have been demonstrated in migraine. Chemopathology and endocrine pathology have not yielded any generally accepted evidence as yet. None other than transitory abnormalities has ever been demonstrated.

## SYMPTOMS AND SIGNS

Probably because of the prominence of headache in the syndrome, it is often forgotten that migraine is a fairly characteristic symptom-complex. As a result of inadequate diagnosis, many inappropriate theories have been proposed and much therapy doomed to failure. The characteristics of migraine are well known. The reliability of diagnosis depends upon the number and prominence of these characteristics in any given case.<sup>12</sup> They are:

1. Recurrent incapacitating headaches occurring against a background of relative well-being. The headaches are usually unilateral at the onset, frequently unilateral throughout the attack, usually temporal, temperoparietal, or frontal but not exclusively so. Though usually throbbing at onset they often become constant as the attack develops. (Periodicity is essential to diagnosis except in infrequent instances of temporary migraine status.)

2. Relief by parenteral ergotamine tartrate occurs

repeatedly in about 90 per cent of the cases and hence approaches a diagnostic test. Cases not relieved by parenteral ergotamine are suspect.

3. Temporary visual disorders precede the headache such as scintillating scotomata (50 per cent) and/or hemianopsia, less characteristic scotomata, photophobia, and frequent but least characteristic "blurred vision."

4. A family history of migraine (70 per cent), frank allergy (30 per cent), or epilepsy (10 per cent) in the patient's immediate family is important. Less significance is put upon their occurrence in distant relatives or upon the presence of neurotic tendencies in immediate or distant relatives.

5. An obsessive tensional personality structure is frequent. This is characterized by perfectionistic inelastic attitudes, considerable drive and ambition hampered by doubts, repetitions, meticulous tendencies, and poorly recognized resentment. There is usually sexual maladjustment, especially in women. These defects are covered by a veneer of poise and social grace.

6. Nausea, vomiting, and retching usually occur at the height of the attack, and characteristically terminate the headache phase.

Less frequently one encounters temporary paresthesias or weakness, speech disorders, and hyperacusia. These are of considerable diagnostic value when they do occur, but at the same time necessitate exclusion of intracranial tumors, aneurysms, etc. Other symptoms occur frequently enough to be considered part of the syndrome but are too protean to be of diagnostic value. These are: vertigo, tinnitus, giddiness, sweating, flushing or paling, chilliness, diuresis, abdominal or thoracic pain, tremor, nuchal rigidity, hallucinations of taste or smell, syncopal and occasionally epileptoid episodes.

#### MIGRAINE TYPES AND VARIANTS

"Red" and "white" migraine as commonly defined, are merely those types in which facial flushing or paling happen to be a prominent feature. This does not allow of the assumption that the entire mechanism in the first type is vasodilator, parasympathetic, or cholinergic or that in the latter it is vasoconstrictor, sympathotonic, or adrenergic. Such an assumption has led to much confusion and therapeutic disappointment. Both paling and flushing may occur in the course of a single attack.

On the other hand, if one limits "red" migraine to the vasodilator, histamine-sensitive group which is relieved by "desensitization," and "white" migraine to the vasoconstrictor type which is histamine-insensitive

and relieved by nicotinic acid, the use of these terms would seem more reasonable.<sup>5</sup>

"Menstrual migraine" is another dubious type in which a close relationship between the headache and the menstrual cycle has led to inconclusive speculation concerning its etiology and therapy. In women with characteristic migraine it was found that in only 10 per cent was there an exclusive relationship between the menstrual cycle and the attacks of migraine.<sup>8</sup> It must be remembered that women are more apt to be irritable at the time of each menses and are more susceptible to both endogenous and exogenous influences.

"Ocular migraine" is headache of proved ocular origin simulating migraine. It is not usually characteristic when carefully analyzed. In these cases the etiology is extra- or intra-ocular imbalance, refractive errors, aniseikonia, and similar disorders.

"Ophthalmoplegic migraine" is probably a form of recurrent oculomotor paralysis with headache and not a form of migraine. The oculomotor palsies may become permanent, and brain-stem lesions have been demonstrated.<sup>13</sup> Aneurysms may at times be responsible for the syndrome.

"Facioplegic migraine" is recurrent facial palsy with headache, and is often merely a coincidence.<sup>13</sup> At other times it may indicate organic pathology such as aneurysm, tumor, infection, etc. It would be dangerous to accept these cases as benign recurrent episodes without exhaustive study.

"Cardiac," "thoracic" and even "pelvic" migraine have been described in which cardiac, thoracic, or pelvic symptoms occur with headache, alternate with headache, or are even said to occur without headache. These types would appear to be rather tenuous when occurring without headache, even in the presence of a migrainous family history.

"Precordial migraine" is a more acceptable syndrome characterized by dull, heavy "pain around the heart" sometimes with radiation to the axilla or left arm without any evidence of demonstrable disease which might reasonably account for left thoracic pain. It usually appears as a "substitute" for headache. It has been reported to be present in 27 per cent of 880 patients with migraine.<sup>14</sup>

"Abdominal migraine" when defined as recurrent episodes of abdominal pain associated with migraine, substituting for migraine attacks, or alternating with such attacks and occurring in migrainous families would seem to be an even more substantial entity.<sup>13</sup> Such episodes are not common but have been seen frequently enough to warrant careful consideration in diagnosis of vague recurrent abdominal distress.



"Ophthalmic migraine" consists of ocular manifestations of migraine such as recurrent scintillating scotomata and hemianopsia, without headache. These episodes sometimes occur as "formes frustes" in persons subject to more characteristic migraine.

Psychic equivalents are episodes of mood lability sometimes with confusion, obsessions, and even brief psychotic episodes occurring in migrainous individuals. They should be differentiated from psychomotor epileptic equivalents by electroencephalography.

Ménière's syndrome sometimes substitutes for an occasional attack of migraine. In some cases it may eventually replace the migraine. The similarity of the two disorders has recently been stressed.<sup>5</sup>

**Migraine Status.** In certain individuals the periodic attacks of migraine may fuse into a continuous episode which may be prolonged for days and is usually characterized by excessive gastro-intestinal symptoms. These episodes are fortunately infrequent. They may follow a period of unusual psychogenic strain.

### COURSE

Migraine is a paroxysmal remissive syndrome. It may increase or decrease in frequency and severity. It often ceases after the first few months of pregnancy returning after lactation ceases. It is usually, but not invariably, self-limited at the climateric.

### DIFFERENTIAL DIAGNOSIS

Brain tumors, especially those of the cerebral surfaces and lateral ventricles, must be excluded by history or the usual tests, before a diagnosis of migraine may be seriously considered. *Fundoscopic examination must be performed on every patient* before continuing with other studies. *Cerebral aneurysms* may simulate migraine for years before they reveal themselves by recognizable hemorrhage. When suspected, careful neurologic examination, cranial roentgenography, and often angiography are indicated.

**Histamine cephalgia** (Horton's histamine headache) should not be confused with migraine. It is characterized by sudden onset and termination of severe unilateral pain in the temple which is increased by vasodilators, such as alcohol, decreased by vasoconstrictors such as adrenalin, reproducible by injection of histamine, and associated with lacrimation and congestion of the eye, eyelids, and nose on the side of the pain. It is not accompanied by gastric symptoms. The syndrome usually occurs in patients over 40 years and the attacks are more frequent at night. Treatment is by histamine "desensitization."<sup>15</sup>

Other disorders to be considered are: Temporo-mandibular,<sup>16</sup> temporal, occipital, and supra-orbital neuralgias;<sup>17</sup> recurrent sinus headache,<sup>18</sup> hypertensive headaches, temporal arteritis,<sup>19</sup> and aniseikonia.<sup>20</sup> Tic douloureux is rarely confused with migraine. Transition forms of Ménière's syndrome may occasion some difficulty. The vasomotor mechanism may be very similar in both.<sup>5</sup>

The most common differential problems occur in *neurotic individuals* and *during the menopause*. These situations may occur singly or combined and require considerable care in eliciting and evaluating the history. Although migraine may occur during the menopause or in neurotic personalities, nonspecific headaches are far more common. It is in such instances that one must keep in mind the relative reliability of the various characteristics of migraine.

Psychic equivalents require a careful history and at times electroencephalography to differentiate them from psychomotor epilepsy.

### COMPLICATIONS

Complications due to migraine itself are rare. There have been a few circumstances in which an hemianopsia has become permanent after an especially severe attack, presumably due to vascular thrombosis.

Most of the "complications" of migraine are due to errors in treatment, which are discussed under that heading, or are due to errors in diagnosis. In the latter group complications due to ruptured aneurysms or other types of unrecognized tumors are most common. Sinus complications, brain abscesses, the development of glaucoma, and other disorders are also to be considered. Careful differential diagnosis should prevent these "complications."

### TREATMENT

**Eugenic.** In order to prevent any disorder with a strong hereditary tendency, the proper selection of a mate is obviously quite important. When selection is possible it would seem unwise for migrainous individuals to procreate if the prospective partner is also unstable. Migraine, epilepsy, and strong allergic tendencies are danger signals in partner or parents. Nevertheless, many talented persons have been born of migrainous parents though they themselves often suffered likewise.

**Preventive therapy** is always desirable but in the case of migraine too often unobtainable. Psychotherapy is helpful in all cases, curative in many. Psychoanalysis

has been effective but is not available to the majority of patients. Narcoanalysis has been helpful in a limited number. It is not likely that electroconvulsive therapy would be very successful in obsessive tensional states but has not yet received a fair trial. The most practical type of psychotherapy in migraine is personality readjustment by a well informed physician. This consists of several phases merging one into the other: 1. Personality study, by means of interviews. 2. Correlation for the patient of his personality reactions and his complaints. 3. Advice concerning change in attitude and habits, and modification, acceptance, or avoidance of unhealthy environmental situations. By this method the physician does not hope or promise to remove all obstacles, endogenous or exogenous. He may, however, help the patient to adjust to reality in a manner which does not call for continual conflict and resultant tension.

At the very beginning, a brief simple explanation of the relationship between emotions and bodily states is of great value in obtaining rapport and understanding. The "blush" is an excellent example of psychosomatic reaction which may be used to explain vasomotor reactions, for example, "A blush *inside* the head is a headache." For detailed instructions on the technic of psychotherapeutic interviews the physician is referred to the brief and excellent discussions by Wolff and by Whitehorn.<sup>7, 21</sup>

**Endocrine Therapy.** In considering any endocrine therapy which has been recommended for migraine, it is wise to examine closely the type of patient relieved thereby. Much of the so-called "migraine" relieved by endocrine therapy would appear to be non-specific headache.

**Estrogenic therapy** has been most successful in the ten per cent of women with migraine in whom there was a definite migraine syndrome and an exclusive menstrual relationship.<sup>8</sup> Emmenin (Collip's estrogenic placental complex) one tablet or one teaspoonful three times a day, doubling the dose one week before and during the menses, was most effective. Premarin (conjugated estrone sulphate from pregnant mares' urine) has not yet been given sufficient trial in migraine. Estradiol dipropionate 1 mg. intramuscularly for seven days premenstrual has been recommended. Stilbestrol, Theelin, Progynon-B and Antuitrin S have been disappointing.

*Induction of the menopause by any means can not be recommended.*<sup>9</sup>

**Allergic therapy** has varied results in various hands. As the responsible allergen is usually ingested or "endogenous" it is difficult to discover. Relief has been obtained, however, by avoidance of, or desensi-

tization to, culpable proteins. Too often the results of therapy are disappointing. It should be borne in mind that psychosomatic reactions may easily be misinterpreted as allergic.

Among the vasomotor therapies, histamine desensitization would appear to be worthy of trial (and further study). The method does not "desensitize" as histamine is not antigenic. The infusions probably increase body tolerance to histamine, stimulate histaminase formation, or alter the vasomotor lability inherent in migraine. Histamine appears to be effective in both those who do, and those who do not overreact to its intradermal injection (0.01 mg. of base). Treatment consists of five or more intravenous infusions of 1 mg. of histamine base (as 2.75 mg. histamine phosphate) in 1,000 to 500 cc. of normal saline solution. Infusions are administered as slowly as possible at first, gradually increasing the rate on successive days, always keeping it slow enough to prevent headache, severe flushing, tachycardia, or significant fall in blood pressure. The patient should sip 200 to 400 cc. of milk with 2 ounces of Amphogel during the infusions to prevent gastric damage.

Histaminase has not proven effective in treatment of migraine.

Prostigmine "desensitization" has been used in a small series of cases with fair results but needs further trial before it may be recommended.<sup>22</sup>

Potassium thiocyanate has been effective in preventing migraine with or without hypertension, but as yet should be restricted to use in appropriate clinics because of its potential danger and the necessity of obtaining blood cyanate determinations at frequent intervals. Doses sufficient to maintain a blood concentration of 2.5 to 8 mg. cyanate per 100 cc. were adequate to control headache. The daily dose is from 195 to 390 mg. (3 to 6 grains) orally with another 390 mg. (6 grains) in the preheadache phase when possible. Headaches due to hypertension per se should not be confused with migraine in evaluating results.<sup>23</sup>

Nicotinic acid has reportedly been successful in terminating and preventing migraine, migraine-Ménière transition forms, and Ménière's syndrome.<sup>5, 24, 25</sup> From six to eight intravenous injections are given daily, starting with 20 to 30 mg. and increasing by daily amounts of 5 mg. to a maximum of 50 mg. after which the patients self-administer 25 to 50 mg. every one to three days intramuscularly also taking 50 to 150 mg. orally during and after the initial treatment, as long as necessary.

Vitamin therapy has been restricted to the B group (although 500 mg. of ascorbic acid intravenously will terminate many headaches). "The action of vitamin

B in migraine is obscure," but good results have reportedly been obtained in more than 65 per cent of a large series of cases.<sup>26</sup> Treatment consists of intramuscular injection of 30 to 100 mg. of thiamine chloride per day for four weeks in the severe cases. After the fourth week 30 mg. is given three times a week for two weeks, then once or twice a week for two or more months increasing or decreasing the amount as seems necessary. (When given intravenously it is diluted to 10 mg. per cc. of distilled water.) In addition to thiamine, an oral dose of 50 mg. of nicotinic acid and 2 mg. of riboflavin is given daily together with "large doses" of the B complex in capsules or syrup. Treatment should be continued for three to six months before it is abandoned as ineffective.

Surgery in migraine should be a last recourse except in well localized unilateral temporal or occipital headaches. In such instances arterial ligation may be indicated if other methods are ineffective. Ligation and section has been performed on the temporal, occipital, and middle meningeal arteries and even upon the external carotid artery, all with satisfactory results. The improvement, however, does not last more than a year. Sympathetic surgery, using various approaches to the problem has been recommended but has fallen into disuse for lack of consistently successful results.

Various diets have been used such as high calcium, ketogenic, low carbohydrate, low fluid, etc., with results often depending on the change in routine, "security of treatment," suggestion by and enthusiasm of the therapist. *Calcium lactate and potassium chloride* in a ratio of 300 to 225 have recently been recommended in an attempt to mobilize extracellular fluid, suppress diuresis, and compensate for fluctuations in arterial blood volume.<sup>27</sup> Highly successful results have been reported in a series of 150 patients who were given 10 grains of the Ca-K mixture daily, increasing to 30 grains daily in one week, continuing at this level for one month and then maintaining a dosage of 10 grains per day with 20 grains every hour in the face of an impending headache. Further observations are necessary.

Abortive therapy may be effective whenever there is sufficient warning of an impending attack. Relaxation and reassurance are essential. The latter entails confidence in the therapist and the routine. Rest in bed, quiet, dim light, and 65 to 195 mg. (1 to 3 grains) of sodium amytal by mouth are useful. Warm baths every three hours may be used. Inhalation of seven liters per minute of 100 per cent oxygen, 3 to 5 mg. of ergotamine tartrate sublingually, 390 mg. (6 grains) of potassium thiocyanate orally or 100 mg. of nicotinic acid intravenously may prove effective.

Symptomatic therapy varies according to the predominant symptoms, the severity of the episode, and the individual reaction. Nonspecific analgesics are used most commonly. In a *mild attack* a cold compress, 0.65 Gm. (10 grains) of acetylsalicylic acid with or without 0.32 Gm. (5 grains) of caffeine may be sufficient to terminate the headache. As it has been demonstrated that equivalent doses of acetanilid, acetphenetidin, and amidopyrine singly or combined are no more effective than acetylsalicylic acid, hence their use is not recommended.<sup>28</sup> *Moderate episodes* require 30 to 60 mg. (1/2 to 1 grain) of codeine or 100 mg. of Demerol (ethyl-1-methyl-4-phenyl-piperidine-4-carboxyl hydrochloride) usually with acetylsalicylic acid. Intravenous injection of 5 cc. of 50 per cent magnesium sulphate is occasionally effective. *Severe attacks* usually require 2 to 3 mg. (1/32 to 1/20 grain) suppositories of Dilaudid (dihydromorphine hydrochloride) or subcutaneous injection of 10 to 15 mg. (1/6 to 1/4 grain) of morphine sulphate. As these substances are habit forming they should be avoided except in "emergencies" when other methods of treatment are not available.

SPECIFIC NONANALGESICS are preferable, especially the vasoconstrictors. Among these the ergot derivatives are most effective.

*Ergotamine tartrate* (Gynergen-Amer., Femergin-Brit.-Sandoz) despite its undesirable side effects remains the most reliable means of terminating attacks of migraine. It has been effective in nearly 90 per cent of 600 cases.<sup>29</sup> It acts by damping the pulsations of the cranial arteries (predominately those derived from the external carotid), by direct vasoconstrictor action on the vessel walls. It acts best when given early in an attack but has no value as a prophylactic agent.

Parenteral injections are thoroughly effective in over 90 per cent of the cases. Although intravenous injections afford rapid relief they should be used only under the direct and continuous supervision of a physician. No more than 0.25 mg. of ergotamine should be given at the first injection. This may be supplemented by a simultaneous subcutaneous injection of another 0.25 mg. Subcutaneous or intramuscular injection is most practical for routine use. The average effective dose is 0.5 mg. Results should be manifest within 30 to 45 minutes. The patient may be instructed in self-administration of the drug, for which the Busher automatic injector is quite helpful. After ascertaining the effect of 0.5 mg. on several occasions, the dose should be progressively decreased to the minimal effect dose.

Oral administration is effective in from 40 to 70 per cent of the cases. Approximately ten times the

parenteral dose is necessary in order to obtain sufficient absorption after ingestion. Thus the average oral dose is 5 mg. The entire five 1 mg. tablets should be swallowed at one time. In cases wherein additional ergotamine is necessary, it may be ingested at the rate of 2 mg. per hour until a total of 9 to 11 mg. has been taken. If the tablets are crushed and allowed to dissolve beneath the tongue, their effect is more rapid and more complete than when ingested. Sublingual administration usually requires less drug, i.e., 3 mg. sublingually is the approximate equivalent of 5 mg. P.O. Because of the taste of ergotamine, not many patients care for this form of therapy. Neither method of oral administration is of any value when vomiting is a prominent part of the syndrome. Whenever oral treatment must be extended over three hours, the subcutaneous route is preferable.

Although many patients have taken ergotamine over long periods of time without untoward effect, certain precautions should be taken. No more than 0.25 mg. should be given intravenously in any single dose, nor more than two such injections in any day. No more than two parenteral injections of ergotamine should be given in any single week, nor more than six per month. Continuation of such rates of administration is *not* advisable. No more than 11 mg. should be ingested in any one day, nor more than 11 mg. three times a week. Daily doses of any amount are to be avoided.

Unpleasant side effects of ergotamine are most common after intravenous injections and least so after oral administration. Nausea or vomiting is the rule after parenteral administration and may occur after ingestion. These symptoms may be relieved by injection or sublingual absorption of 0.65 mg. (1/100 grain) atropine sulphate before or during the administration of ergotamine. "Cramps" along the course of the main arteries in the arms and legs occur occasionally after parenteral injection. They are rapidly relieved by massage or exercise. Temporary paresthesias of the fingers and toes are frequent but should cause no alarm. Persistent paresthesias suggest the possibility of early ergotism and contraindicate the further use of ergotamine until ergotism is excluded by examination. Substernal oppression may occasionally alarm the patient. In the absence of organic heart disease, this need not distress the physician. Occasionally cardiac symptoms may be severe enough to prevent the use of ergotamine.

Serious sequelae to the use of ergotamine are rare. "Contraindications to the use of ergotamine are septic states, especially when associated with intravascular

foci; and obliterative vascular diseases, especially when coronary."<sup>30</sup>

*Ergonovine* (Ergobasine, Sandoz; Ergoklonin, Wyeth; Ergotrate, Lilly; Ergometrine, Burroughs-Wellcome) is less effective than ergotamine, although the reverse is occasionally true when administration is by the oral route.<sup>20</sup> It causes less nausea and vomiting than ergotamine and is also useful in patients who complain of severe paresthesias following ergotamine. Ergonovine is contraindicated during pregnancy because of its strong oxytocic action. The dosage and method of administration are the same as for ergotamine.

*Dihydro-ergotamine Methanesulfonate* (D.H.E.-45, Sandoz) is a recent ergot extract in which the vasoconstrictor factor has been retained while the oxytocic factor has been eliminated. Theoretically, it should be more effective per gram than ergotamine. Actually it has proved to be very effective but must be given in doses twice as great as Gynergen. As yet it is available only for parenteral injection in 1 cc. ampules containing 1 mg. D.H.E.-45 per cc. (Gynergen contains 0.5 mg. of ergotamine tartrate per cc.). Of prime importance, however, is that the toxicity of Gynergen is from five to ten times greater than D.H.E.-45. The latter drug may be given by the intramuscular or intravenous route in 1 cc. (1 mg.) dose with impunity and has been given in 2 to 3 cc. intramuscular doses without untoward results. It has little if any oxytocic effect and has been given to a few cases during the early months of pregnancy without ill effects. Its unpleasant side effects, when they do occur, are the same as those of Gynergen. Good to excellent results have been reported in from 70 to 90 per cent of 150 cases following intramuscular injection of 1 mg.<sup>31</sup> It has been suggested that if 2 mg. were used results might be as good as those obtained by ergotamine with fewer undesirable reactions.

*Adrenaline* (1 cc. of 1:1,000 solution subcutaneously), *ephedrine* (3/4 grain subcutaneously), and *epinephrine* have been used in small series of patients with inconclusive results. Intravenous injection of 3 to 30 mg. of *Benzedrine* sulphate (amphetamine sulphate) at 1 mg. per minute has been used successfully in a small group of cases. Relief was obtained in from 7 to 45 minutes in 67 per cent of 18 cases.<sup>32</sup> Among other substances recommended for their supposed vasoconstrictor action, the following may be mentioned but not recommended: Subcutaneous Pituitrin (0.5 cc.), intravenous 10 per cent solutions of sodium chloride or 20 per cent solutions of glucose and intravenous injection of 0.5 Gm. 7½ grains) of caffeine sodium benzoate.

The inhalation of seven liters per minute of 100 per cent oxygen from one-half to two hours has reportedly been effective in a considerable number of cases.<sup>23</sup> The best means of administering this percentage is by means of a Boothby mask.

*Vasodilators* such as trichlorethylene, amyl nitrite, erythroltetranitrate, nitroglycerine, intravenous magnesium sulphate, intramuscular acetylcholine (0.1 Gm.) or Mecholin (acetyl-beta-methyl-choline-chloride) in 15 mg. dose, and even 0.5 cc. of 1:1,000 histamine solution subcutaneously, have been used in migraine. It has been reported that each of these has terminated occasional episodes of migraine, although all are capable of inducing headache. It may be that they "abort" attacks in the primary vasoconstrictor phase or lower the blood pressure sufficiently to dampen the arterial pulsations of the second phase. They are not recommended for routine use.

*Octin* (methyl-iso-octenylamine) has been said to have terminated attacks in a small number of patients and also to have some prophylactic value.<sup>26</sup> The drug is said to act directly on smooth muscle and by stimulating inhibitory sympathetic fibers with resultant vascular relaxation. The prophylactic dose is 130 mg. (2 grains) of Octin mucate orally three times a day. When used to terminate attacks, 100 mg. of Octin hydrochloride are given intramuscularly and repeated in two hours if necessary.

*Nicotinic acid* in intravenous doses of 100 mg. has recently been reported to have given complete relief to various types of headaches within two minutes after injection.<sup>25</sup> Migraine headaches have been among those relieved. It may be given as its equivalent in sodium salt.

### ADJUVANT THERAPY

The gastric symptoms of migraine are often relieved by a rectal suppository of 130 to 195 mg. (2 to 3 grains) of Nembutol (sodium ethyl-methyl-butyl-barbiturate), or by 65 to 195 mg. (1 to 3 grains) of sodium amytal if given early enough to prevent vomiting. Atropine sulphate sublingually or subcutaneously in doses of 0.5 to 0.6 mg. (1/120 to 1/100 grain) usually controls the nausea and vomiting, due not only to the migraine but also that due to use of ergotamine.

In the treatment of migraine status reassurance and confidence in the routine or practitioner, are essential. Relaxation should also be induced by other means, such as a warm bath and sedation with sodium amytal orally in 3-grain doses three times a day or light intravenous narcosis. Oral medication is usually ineffective because of vomiting. Ergotamine has been successful

in parenteral doses of 0.5 mg. each twice a day for one day but should not be continued longer. Intravenous nicotinic acid in 100 mg. doses should be effective. Rectal sedation as outlined in the previous section is helpful in reducing the gastric symptoms. Oxygen inhalation is occasionally useful. At times, fluids must be replenished by infusions or clysis despite the discomfort occasioned thereby. Morphine is to be avoided.

### PROGNOSIS

The prognosis in migraine varies with its causal relationships, and the type of therapy employed. Thus the prognosis depends not only on the disorder itself but upon the acumen and persistence of the physician. In general it is a self-limited disorder often ceasing with the climacteric (male or female). It is never fatal unless by suicide or therapeutic error. Those types in which there is a strong hereditary factor are less tractable. Personality adjustment and confidence in the physician and his therapy seem to offer the best prospect for an earlier termination. All patients can be helped; too few are permanently cured.

### BIBLIOGRAPHY

1. Schumacher, G. A., and H. G. Wolff: Experimental studies on migraine. A. Contrast of histamine headache with the headache of migraine and that associated with hypertension. B. Contrast of vascular mechanisms in preheadache and in headache phenomena of migraine, *Arch. Neurol. & Psychiat.*, 45: 199, 1941.
2. Torda, C., and H. G. Wolff: Experimental studies on headache. Transient thickening of walls of cranial arteries in relation to certain phenomena of migraine headache and action of ergotamine tartrate on thickened vessels, *Arch. Neurol. & Psychiat.*, 53:329, 1945.
3. Simons, D. J., E. Day, H. Goodell, and H. G. Wolff: Experimental studies on headache: muscles of the scalp and neck as sources of pain, *Research Publ. A. Nerv. & Ment. Dis.*, 23:228, 1943.
4. Ray, B. S., and H. G. Wolff: Experimental studies on headache. Pain sensitive structures of the head and their significance in migraine, *Arch. Neurol. & Psychiat.*, 41:813, 1940.
5. Atkinson, M.: Ménière's syndrome and migraine: observations on a common causal relationship, *Ann. Int. Med.*, 18:797, 1943.
6. Morlock, C. G., and W. C. Alvarez: Has disease of the liver anything to do with the causation of migraine?, *J. A. M. A.*, 114:1744, 1940.
7. Wolff, H. G.: Migraine. *Modern Medical Therapy in General Practice*, Baltimore, Williams & Wilkins, 1940, p. 2068.
8. Price, J., and T. J. C. von Storch: Endocrine abnormalities and oestrogen therapy in 200 women with migraine (Unpubl. data).

9. Alvarez, W. C.: Can we cure migraine in women by inducing menopause? Report on 42 cases, Proc. Staff Meet. Mayo Clin., 15:380, 1940.
10. von Storch, T. J. C., and E. M. Follensby: Analysis of the role of allergy in 862 reported cases (Unpubl. data).
11. (a) Unger, L.: Migraine reproduced by injections of specific allergens, J. Allergy, 12:197, 1940.  
(b) Wolff, A. A., and L. Unger: Migraine due to milk: feeding tests, Ann. Int. Med., 20:828, 1944.
12. von Storch, T. J. C.: Diagnostic criteria of migraine (Unpubl. data).
13. Riley, H. A.: Migraine, Bull. Neurol. Inst. New York, 2:429, 1932.
14. Fitz-Hugh, T., Jr.: Precordial migraine: An important form of "angina innocens," Intern. Clinics, 1:143, 1940.
15. Horton, B. T.: The use of histamine in the treatment of specific types of headache, J. A. M. A., 116:377, 1941.
16. Costen, J. B.: Some features of mandibular articulation as it pertains to otolaryngology, Int. J. Orthodont., 22:1011, 1936.
17. Harris, W.: The Facial Neuralgias, London, Oxford, 1937.
18. Sluder, G.: Nasal Neuralgia, Headache, and Eye Disorders, St. Louis, Mosby, 1927.
19. Kilbourne, E. D., and H. G. Wolff: Cranial arteries: a critical evaluation of the syndrome of "temporal arteritis" with report of a case, Ann. Int. Med., 24:1, 1946.
20. Bannon, R. E.: Headaches and aniseikonia, Am. J. Optometry, 17:1501, 1940.
21. Whitehorn, J. C.: Guide to interviewing and personality study, Arch. Neurol. & Psychiat., 52:197, 1944.
22. Perner, L., and M. E. Aibel: The treatment of severe periodic headache with "desensitizing" doses of prostigmine, J. Lab. & Clin. Med., 27:1546, 1942.
23. Engle, D. E., and C. O. Evanson: The effect of potassium thiocyanate on the occurrence of migraine, Am. J. Med. Sci., 204:697, 1942.
24. Atkinson, M.: Migraine headache: Some clinical observations on the vascular mechanism and its control, Ann. Int. Med., 21:990, 1944.
25. Goldzieher, J. W., and G. I. Popkin: Treatment of headache with intravenous sodium nicotinate, J. A. M. A., 131:103, 1946.
26. Palmer, H. D.: Migraine headache, Clinics, 4:531, 1945.
27. Pfeiffer, C., R. H. Dreisbach, C. C. Roby, and H. G. Glass: Etiology of migraine syndrome—physiologic approach, J. Lab. & Clin. Med., 28:1219, 1943.
28. Wolff, H. G., J. D. Hardy, and H. Goodell: Measurement of the effect of acetylsalicylic acid, acetanilid, acetphenetidine, amidopyrine, ethyl alcohol, trichlorethylene, a barbiturate, quinine, ergotamine tartrate, and caffeine. An analysis of their relation to the pain experience, J. Clin. Invest., 20:63, 1941.
29. von Storch, T. J. C.: On the treatment of migraine, Med. Clin. N. Amer., 25:1317, 1941.
30. von Storch, T. J. C.: Complications following the use of ergotamine tartrate. Their relation to the treatment of migraine headache, J. A. M. A., 111:293, 1938.
31. (a) Horton, B. T., G. A. Peters, and L. S. Blumenthal: A new product in the treatment of migraine, Proc. Central Soc. Clin. Res., 15:91, 1942.  
(b) Friedman, M. D., and D. A. Friedman: Dihydroergotamine (D.H.E.-45) in the treatment of migraine. Preliminary clinical observations, Ohio State Med. J., 41:1099, 1945.  
(c) Hartman, M. D.: Parenteral use of dihydroergotamine in migraine, Ann. Allergy, 3:440, 1945.  
(d) Dannenberg, T.: Comparison of dihydroergotamine, ergotamine, and other agents in the treatment of migraine, Permanente Foundation M. Bull., 4:96, 1946.  
(e) Klein, N. W.: D.H.E.-45 (dihydroergotamine) in the treatment of allergic migraine, Ann. Allergy, 4:128, 1946.
32. Gottlieb, J. S.: The effect of Benzedrine sulphate on migraine, Am. J. Med. Sci., 204:553, 1942.
33. Alvarez, W. C., and A. Y. Mason: Results obtained in the treatment of headache with the inhalation of pure oxygen, Proc. Staff Meet. Mayo Clinic, 15:616, 1940.

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Dr. G. H. A. Clowes, Ph.D., Sc.D., LL.D., Director Emeritus of the Lilly Research Laboratories, was honored by the American Diabetes Association at its recent annual meeting in Atlantic City, New Jersey. He delivered the annual Banting Memorial address and was awarded the Banting Medal which is given in recognition of distinguished service in the field of diabetes.

Under Dr. Clowes' direction, the Lilly Research Laboratories co-operated with the University of Toronto and Drs. Banting and Best in the early development of insulin of sufficient purity and stability to permit its widespread clinical use throughout the world.

*This paper emphasizes the necessity of ophthalmoscopy in the study of hypertension. It can be said with little cause for contradiction that the ophthalmoscope ranks with the sphygmomanometer in reaching decisions on treatment and prognosis in the modern care of the hypertensive patient.*

## Interpretation of Ophthalmoscopic Findings in Arterial Hypertension

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Gowers<sup>1</sup> in 1876 called attention to the importance of the ophthalmoscope to the physician in obtaining information regarding the state of the terminal arteries and veins. He also maintained that, excluding ocular and cerebral diseases, changes in the state of retinal vessels may be taken as evidence of similar changes throughout the vascular system. He demonstrated that narrowing of the retinal arteries occurs quite independently of retinal pathology and stands commonly in direct relation to the blood tension; that in Bright's disease the diminution in size of the retinal arteries depends upon contraction, and that the contraction of the arteries seen in the retina is inferred to exist elsewhere and is, in part at least, the cause of the increased blood tension. He stressed the value of ophthalmoscopic examination of the retinal vessels in an effort to distinguish between the morbid states included under the term "Bright's disease."

In 1890 Hirschberg<sup>2</sup> stated that diffuse opacities of the retina around the opaque optic nerve head, dilatation of the retinal veins and contraction of the arteries characterize albuminuric retinitis. He was the first to describe irregularities of the lumen of the retinal arteries in this condition.

Volhard<sup>3</sup> propounded the theory that albuminuric neuroretinitis is the result of an ischemia which depends not invariably upon direct changes of vascular walls, but on states of contraction which may later be accompanied by proliferations of vascular endothelium. All other changes in the retina are secondary to arterial ischemia. Manifestations of ischemia in the guise of marked attenuation of the branches of the central artery are observable in all cases, and in many instances precede retinal changes. The ischemia, if protracted, may induce renal insufficiency. Schieck believed Volhard's theory to be correct, since it was in almost complete accord with his own anatomic, pathologic and clinical experiences.

Volhard<sup>4</sup> agreed with Schieck<sup>5</sup> that there was a definite relation between elevation of blood pressure and albuminuric retinitis, but differed from him as to the mode of production. Schieck believed there was an excess of blood in the retina, while Volhard be-

lieved there was a deficiency of blood. Volhard felt that hypertension which did not exhibit an albuminuric retinitis should be diagnosed essential hypertension or benign nephrosclerosis, while that exhibiting albuminuric retinitis should be designated as the combined form or malignant nephrosclerosis. He stated that what Benedict<sup>6</sup> called hypertension plus nephritis and Wagner<sup>7</sup> designated malignant hypertension is this combined form of malignant sclerosis of Volhard. He pointed out that the benign form terminates in cardiac disease and the malignant form in renal failure (uremia). This caused Volhard to believe that the mechanism of increase of blood pressure must be definite in both instances. Cases of benign nephrosclerosis or essential hypertension may pass into a malignant form or into the condition of sclerosis plus nephritis. Volhard<sup>8</sup> believed that the renal changes in nephritis were the result of a general vascular contraction which in its turn induced ischemia. He also believed a general angiospasm to be responsible for the condition of the kidney in pregnancy and eclampsia. He quoted the work of Haselhorst and Mylius<sup>9</sup> in support of this belief. Volhard next considered the course of the pathogenic process. In his opinion there was no doubt that it was not the increased blood pressure which physically by pressure of fluid injured the affected organ and its vessels, be it the brain, kidney or retina, but that, on the contrary, it was a disturbance of nutrition in consequence of obstruction of the supply of blood and oxygen. In brief, a severe disturbance of internal respiration occurred. He likened the process to inflammation except that in the latter there is arterial hyperemia and here there is arterial ischemia. Hence, according to Volhard "There can no longer be any doubt that organic changes of arterioles as observed in chronic cases must merely be the result of arterial ischemia . . . and not a result of elevated blood pressure." Volhard compared complete occlusion of arterial blood flow with a partial obstruction of arterial blood flow. In the first instance there was death of the tissues and function ceased; in the second, the tissues survived but function was seriously impeded though not suspended.



From their investigations, Fishberg and Oppenheimer<sup>10</sup> concluded that the traditional unitary concept of albuminuric retinitis, so-called, should be discarded and the three ophthalmoscopic pictures possible in patients suffering with diseases characterized by arterial hypertension should be differentiated into (a) retinal arteriosclerosis and arteriosclerotic retinopathy, (b) malignant hypertensive neuroretinopathy and (c) choked disk due to increased intracranial pressure. They were of the opinion that it is evident that renal insufficiency of itself does not cause retinal lesions. In malignant hypertensive neuroretinopathy arteriosclerosis might be absent if the hypertension was of brief duration. They found necrosis of renal arterioles in all such cases, while increase of intracranial tension occurred in some patients with hypertensive neuroretinopathy, and there were others in whom it was repeatedly normal. Hypertension not only was present in every instance of albuminuric retinitis, but as far as was known, invariably preceded the appearance of retinal lesions. Chronic glomerulonephritis occasionally did progress to renal insufficiency and fatal uremia without the development of retinal lesions. They believed that the presence of malignant hypertensive neuroretinopathy in essential hypertension was diagnostic of necrosis of renal arterioles. However, this did not hold true in glomerulonephritis.

Weinbrenner<sup>11</sup> reviewed Volhard's classification of elevated blood pressure into red high blood pressure, which is unrelated to any form of renal disease and is typically a disease of older people, and pale high blood pressure or nephrosclerosis, which soon leads to renal insufficiency. He stated further that "another observable difference is that red high blood pressure has a typical high systolic pressure, while pale blood pressure has a high diastolic hypertension also. Patients with red high blood pressure die either of apoplexy or of cardiac decompensation, whereas patients with pale high blood pressure mostly die of renal insufficiency." He believed that red high blood pressure was the result of sclerosis of the larger and medium sized arteries, while pale high blood pressure was produced by vasoconstrictor substances originating in the kidney and always resulting from disturbances of renal circulation. He pointed out that many cases of red high blood pressure passed over into pale high blood pressure. Marked pallor of the skin with contraction of the retinal arteries would indicate an angiospasm affecting all parts of the vascular system. According to Volhard, the retinal involvement should be designated angiospastic retinitis. When a red became converted into a pale hypertension, elevation of diastolic pressure and development of retinitis were

the chief indications. All phases of transition might develop and the tempo and course of renal disease could be determined from the severity of the retinal changes.

In late 1946, 70 years after Gowers first called attention to the importance of ophthalmoscopy in determining the state of retinal vessels and, in turn, those of similar size throughout the body, a committee appointed by the American Ophthalmological Society<sup>12</sup> has reported on the classification of retinal lesions in the presence of vascular hypertension. They assert the following:

1. That the arterial vessels seen with the ophthalmoscope should be designated as arterioles.
2. That three distinct types of alteration occur in the retinal arterioles in the different phases of hypertensive disease.
  - a. Generalized narrowing (which represents probably the generally increased tone of the arteriolar system).
  - b. Sclerosis (organic thickening of the wall of the arteriole).
  - c. Focal constriction (spasm).
3. That the term *retinopathy* in hypertensive or renal disease means the involvement of the retina characterized by serous and hemorrhagic extravasations into and under the retina; this serous extravasation may be represented by diffuse edema, by localized "cottonwool" patches, or by the more chronic punctate deposits considered to be the late results or residues of edema and which include "macular star" formation. At times edema of the nerve head occurs in association with the retinopathy. For this combination the terms *neuroretinopathy* or *retinopathy with papilledema* are acceptable.

It was felt that occlusion of either retinal or chorioidal vessels should be so designated and not included under the term *hypertensive retinopathy*, and that the component elements of *retinopathy* are basically identical in all forms of hypertensive and renal disease.

Various combinations of the individual lesions listed as being found in the retina and its vessels make up the ophthalmoscopic picture characteristic of the several classified types of hypertensive and renal lesions. Careful determination of the types of changes visible in the arterioles of the retina is essential for diagnostic and prognostic evaluation of the hypertensive disease.

The interpretation of the severity of arteriolar lesions is important. Practically identical lesions can occur in primary "essential" hypertension and in hy-



pertension secondary to acute or chronic glomerulonephritis, toxemia of pregnancy, etc.

Terms such as *cottonwool patches*, *powdery flecks* and *macular star* are acceptable for descriptive purposes. In order to make a diagnosis of retinopathy the presence of cottonwool patches or edema or edema residues is requisite. Vascular occlusions should be included under lesions of the retinal vessels.

It is recommended that lesions of retinal arterioles be broken down into four grades depending upon the degree of generalized narrowing, focal constriction or focal sclerosis and generalized sclerosis of arterioles.

The committee classified vascular hypertension into the following:

1. Neurogenic hypertension.
2. Acute hypertension (angiospastic).
3. Chronic nonprogressive (benign) hypertension.
4. Chronic progressive hypertension.
5. Terminal malignant hypertension.

In 1940 the author<sup>13</sup> made a clinical and pathologic study of a group of 16 patients with marked arterial hypertension or renal insufficiency. Microscopic studies were made of the viscera and the posterior segment of the eyes. In all tissues the smallest arteries and arterioles were found to have marked medial hyperplasia and, in most instances, hyalinization with narrowing of the lumen, particularly in the arterioles. Cottonwool patches were identified as the result of localized areas of serous exudate in the deeper layers of the retina or cytoïd bodies in the nerve-fiber layer. The fine white areas often arranged in lines radiating from the macula were identified as collections of lipoidal histiocytes, usually in the outer plexiform layer. The flame-shaped hemorrhages were found to involve the nerve-fiber layer, while the more punctate and roundish hemorrhages were in the deeper layers or beneath the retina. The gray, edematous appearance of the retina adjacent to the disk was the result of subretinal serous or fibrinous exudate, and, rarely edema in the nerve-fiber layer. No evidence of inflammation was observed in the retina or the choroid of any of the cases studied.

The one constant ophthalmoscopic finding in arterial hypertension is narrowing of the lumen of the retinal arterioles. This narrowing may be purely spastic with no organic or structural change in the vessel wall. This is the condition which prevails in the so-called neurogenic hypertension or in the acute hypertension associated with eclampsia or the toxemias of pregnancy. In this latter condition the degree of attenuation of the retinal vessels may be much more marked in certain branches of the retinal arterioles than others; however, if the hypertension persists

the narrowing becomes more uniform and it either becomes benign in character or may become a chronic progressive type.

In acute hypertension the fundus changes, in addition to attenuation of the retinal arterioles, consist of cottonwool patches, serous extravasations beneath or into the retina, retinal hemorrhages, papilledema and occasionally macular star formation. This entire picture may vary in degree and may entirely disappear if the cause can be removed before the hypertension has become too definitely established.

Chronic nonprogressive or benign hypertension usually begins in an older age group of individuals. There is never papilledema in this condition. There is narrowing of the retinal arterioles with irregularity of the lumen, arteriovenous compression and there may be an occasional retinal hemorrhage or cottonwool patch. Nevertheless there may never be any fundus changes other than the attenuation and subsequent sclerosis of the retinal arterioles.

Chronic progressive hypertension is characterized by arteriolar narrowing with marked irregularity of the lumen and arteriovenous compression, cottonwool patches, retinal hemorrhages, but neither papilledema nor subretinal serous extravasations. This condition may pass into the terminal malignant phase at which time papilledema and extravasations may develop.

The ophthalmoscopic findings in terminal malignant hypertension include marked attenuation of retinal arterioles with irregularity of the lumen and arteriovenous compression. Cottonwool patches and retinal hemorrhages are usually present, with subretinal serous extravasations and papilledema. There may be the formation of a partial or complete macular star. These findings may vary in degree, depending upon the phase of the disease at the time the examination is made.

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## BIBLIOGRAPHY

1. Gowers, W. R.: Brit. M. J., 2:743, 1876.
2. Hirschberg, J.: Deutsche med. Wchnschr., 16:1236, 1890.
3. Volhard, F.: *Ibid.*
4. Volhard, F.: Zentralbl. f. inn. Med., 48:1, 1927.
5. Schieck, F.: Klin. Monatsbl. f. Augenh., 66:39, 1921.
6. Benedict, W. L.: Am. J. Ophth., 4:495, 1921.
7. Wagener, H. P.: Am. J. Ophth., 7:272, 1924.
8. Volhard, F.: Zentralbl. f. d. ges. Ophth., 21:129, 1929.
9. Haselhorst and Mylius: Quoted by Volhard, Ref. 8.
10. Fishberg, A. M., and B. S. Oppenheimer: Arch. Int. Med., 46:901, 1930.
11. Weinbrenner, H. P.: J. Philippine Islands M. A., 16:27, 1936.
12. American Ophthalmological Society: The Retina in the Presence of Vascular Hypertension, 1946.
13. Greear, James N., Jr.: Trans. Am. Ophth. Soc., 38:397, 1940.

*This simple, practical, and satisfactory method for the home use of penicillin aerosol, suitable for both children and adults, should be useful.*

## Simplification of Penicillin Aerosol Therapy for Home Treatment

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Prolonged administration of penicillin aerosol has proved a valuable therapeutic measure in bronchopulmonary infections. In order to achieve more than temporary results in subacute and chronic conditions, continuation of this treatment in the patient's home for several weeks and even months is necessary.<sup>1</sup>

In the office, compressed air or oxygen is generally used as a nebulizing agent. For use at the patient's home, a hand nebulizer may prove adequate for short treatments. However, for any longer treatment, this cumbersome method requires some endurance in the patient. The time-consuming procedure, and especially the strain on the patient's hand, frequently leads to a relaxation in the correct administration of the antibiotic, and consequently, unsatisfactory therapeutic effects.

Another shortcoming of the current mode of penicillin aerosol therapy is the rather complicated method by which the penicillin must be dissolved in the vial and the required dose taken out for each treatment. Unless carefully done, this procedure makes a certain loss of penicillin unavoidable. Furthermore, to avoid deterioration the remaining penicillin solution must be stored in a refrigerator for succeeding treatments.

For the past two years, this writer has been trying to help his patients continue the treatment at home by inexpensive methods which involve as little inconvenience as is compatible with full therapeutic effect. The best method arrived at makes use of a simple bicycle pump and of penicillin triturate tablets.

Two types of inexpensive hand pumps were found most convenient and efficient for patients who were unwilling or financially unable to use oxygen. The one (Fig. 1) can be attached to a board, thus giving the patient a sufficiently large base to hold the pump with one foot. The other type (Fig. 2) can be fastened within easy reach of the patient, for example, on the chair which he occupies during treatment. The former furnishes a rather high pressure and is most appropriate for adults. The latter is a little less force-



FIGURE 1

ful, but can be handled very easily, even by children. Both are considerably less tiresome and time-consuming than a hand bulb, and, in my opinion, more convenient for the patient than the automobile foot pump suggested by Barach.<sup>2</sup>

In order to prepare the pump for penicillin aerosol administration, the valve at the end of the rubber hose is cut off, and pump and nebulizer are connected by means of rubber tubing. To obtain filtered air for aerolization, a small glass-wool filter can be inserted into the air stream.

The patient holds the nebulizer in one hand, his



FIGURE 2

other hand grasping the pump handle. While inhaling deeply and slowly, he presses the handle down, holds his breath for a few seconds and then empties his lungs through the nose or mouth, withdrawing the handle at the same time. If the larger type pump is used, sufficient pressure is obtained by pressing the plunger only part way down.

Children too young to use the nebulizer directly are treated by means of one of the head tents now commercially available. A head tent can also be improvised from a wooden or metal frame covered with transparent plastic sheet material (Fig. 3). Here, too, a bicycle pump handled by the child's attendant can replace oxygen. The tent is placed over the child, and the nebulizer containing the required amount of penicillin solution connected with the tent. The latter is then filled with the penicillin mist, and the child is left under the tent for about ten minutes following completion of penicillin aerolization. An adequate supply of fresh air under the tent can be assured by allowing some air to enter the tent from the bottom. A slightly larger dose of the antibiotic should be used to compensate for the unavoidable leakage.



FIGURE 3

Instead of penicillin as furnished in vials, triturate tablets are used.\* These provide a fresh supply for each treatment without having to be kept cool. One or more tablets, each containing 50,000 units of crystalline G-penicillin, are put into the nebulizer and 1 cc. distilled water added. Although even four tablets dissolve easily in this amount of water, it is recommended that for more than two tablets, at least 1.5 cc. should be used since highly concentrated solutions occasionally disagree with the patient.

A single treatment of penicillin aerosol following the above outlined method takes from 10 to 15 minutes. This includes the time elapsing before that penicillin which condenses in the nebulizer drops back to the bottom. Although 1 cc. solution can be nebulized in a much shorter time, it should be emphasized that for obtaining the best possible results, any undue efforts to save a few minutes should be discouraged.

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### BIBLIOGRAPHY

1. Finke, W.: The rationale of penicillin aerosol therapy in bronchopulmonary infections, Bull. Med. Soc. County of Monroe, N. Y., 5:9-16 (May) 1947.
2. Barach, A. L., and B. Garthwaite: Physiologic and antibiotic (penicillin) therapy in chronic hypertrophic pulmonary emphysema, Dis. Chest, 13:91-122 (March-April) 1947.

\* The crystalline G-penicillin triturate tablets used were kindly furnished by Commercial Solvents Corporation and Premo Pharmaceutical Laboratories, Inc.

*Rheumatic fever is always a most interesting disease to the clinician because of its great variety of clinical expressions. This paper contains numerous case histories to illustrate the protean nature of the disease.*

## Protean Manifestations of Acute Rheumatic Fever

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It has been estimated that there are about 170,000 new cases of rheumatic fever per year in the United States in times of peace, and a total of 840,000 cases of active and inactive rheumatic heart diseases per 100,000,000 people.<sup>1</sup> These figures have increased during the war years due to a multiplicity of factors and establish the prime importance of this disease as a public health and military problem.

In a large southwestern station hospital servicing a great number of troops, many atypical manifestations of rheumatic fever were encountered. In many instances, the diagnosis was definitely established only after prolonged study. The occurrence of unusual cases was greatly disproportionate as compared with other sections of the country. Soldiers from northern and southern camps came from approximately the same admixture of locations and the hereditaries were so thoroughly mixed that one might assume that there would be just as many susceptible persons in any area. Although a greater percentage of cases actually occurred in the northern camps, milder and more atypical manifestations appeared in the southern camps.

In addition to upper respiratory infections and hereditary background of susceptibility, meteorologic factors apparently played an important role. Paul and Dixon,<sup>2</sup> employing similar racial and age groups (American Indian children), found an incidence of 4.5 per cent with rheumatic heart disease in the northwestern states as compared with only 0.5 per cent in the southwestern states.

The age group, fresh recruits and rigorous outdoor activities were also significant factors. A large proportion of previously unexposed men came from agricultural areas. The additional factors of close proximity during sleeping and messing, droplet infection, occasional occurrence of upper respiratory and acute hemolytic streptococcal pharyngitis epidemics increased the percentage of involvement.

The early diagnosis of rheumatic fever with atypical manifestations is most important. When intensive

salicylate therapy is given early in the disease as outlined by Coburn,<sup>3</sup> recrudescences and residua are materially reduced. Cardiac involvement may be prevented if therapy is instituted before clinically recognizable carditis has appeared; and already existing carditis is favorably influenced.<sup>4</sup> The importance of controlling the ravages of the disease is further heightened by the present prophylactic use of sulfadiazine and new advances in hypersensitivity and immunization.

The following case studies of certain atypical manifestations of acute rheumatic fever stress its protean nature. In addition, certain interesting but confusing allied and nonallied diseases with joint involvement are presented as an aid to differential diagnosis.

### CASE WITH BOTH RHEUMATIC PERITONITIS AND RHEUMATIC PNEUMONIA

#### RHEUMATIC PERITONITIS

As far back as 1839, Andral<sup>4a</sup> called attention to the significance of abdominal pain in acute rheumatic fever, yet reports in the current literature are sparse. Undoubtedly, many cases are overlooked or misdiagnosed. Abdominal symptoms in acute rheumatic fever may occur early and dominate the picture, simulating acute appendicitis.<sup>5-12</sup> Abdominal pain may range in severity from a fairly common mild manifestation in children to severe acute attacks which occasionally result in unnecessary operative interference. The pain usually occurs in the epigastrium or the left upper quadrant and does not radiate. Reitman's<sup>13</sup> four cases presented a right rectus muscle syndrome. Although there may be tenderness, there is usually absence of rigidity. Frequently, attacks may be associated with vomiting and a temperature rise above 101° F. They may recur but generally become milder.

It is also important to exclude acute hepatic enlargement occasionally noted in children during a severe attack of rheumatic carditis. Upper respiratory

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infections may be associated with abdominal pain in children. However, the severe generalized reaction, high fever and leukocytosis (often above 20,000) with localized pain appearing during or just prior to the attacks of rheumatic fever are important differentiating criteria. If doubt persists, exploratory operation is indicated. At the time of operation clear fluid is usually found in the abdomen with hyperemia, edema and infiltration of the peritoneal and subperitoneal tissues, without evident cause.

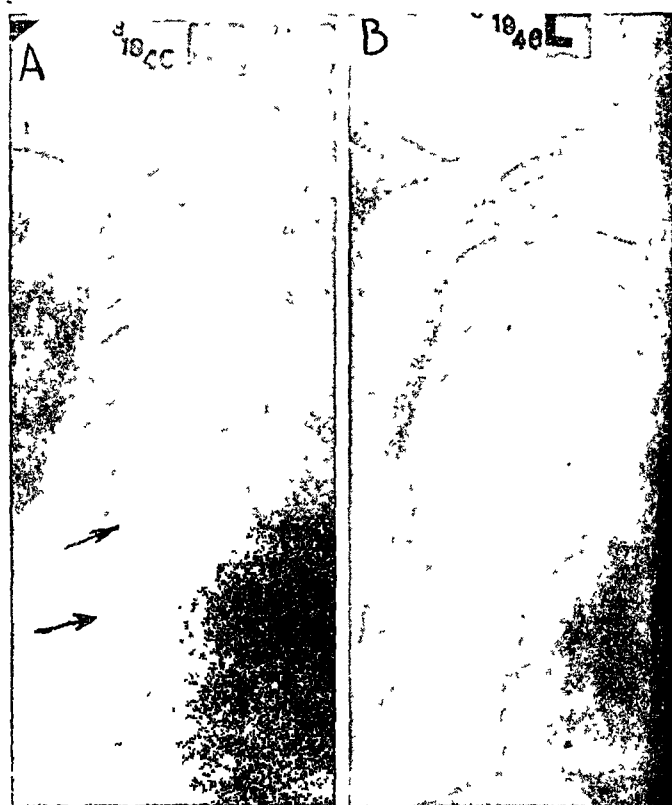


FIG. 1. A. Rheumatic Pneumonia. Irregularly scattered areas of soft infiltrations throughout both lower lungs fields, more marked on the left side. Onset of pneumonic involvement occurred the previous day. B. Marked diminution in extent and intensity of the infiltrations the following day illustrating the transient nature of the exudates.

### RHEUMATIC PNEUMONIA

Pneumonic involvement during an attack of acute rheumatic fever usually occurs at the height of infection. Cough and sputum are not prominent features and the diagnosis usually rests on finding signs of diffuse pulmonary exudation or typical x-ray changes. They are of transient and migratory nature and disappear within a few days. Part of one lobe may be involved or it may extend to all the lobes. Daily x-rays studies illustrate the transient nature of the exudates (Fig. 1). The pathology has been well de-

scribed by von Glahn and Pappenheimer,<sup>14</sup> Naish,<sup>15</sup> and Gouley and Eiman.<sup>16</sup> It consists essentially of irregularly scattered hemorrhagic consolidations.

The following case was unusual in that both glomerulonephritis and pneumonia developed during the course of an attack of acute rheumatic fever. Although the patient gave a past history of rheumatic fever, his presenting complaints were entirely referable to the abdomen. A diagnosis of appendicitis was made and operation performed.

The occurrence of rheumatic involvement of the lungs is well illustrated in the same patient. The beneficial action of intensive salicylate therapy on the pneumonitis is somewhat difficult to evaluate as a therapeutic test since this manifestation is very transient and frequently missed.

**CASE 1.** A white male, aged 17, with three months of service, complained of abdominal pain for one day.

**Antecedent History.** Family history was negative except that his father had chronic rheumatism. The patient had multiple migrating joint pains lasting a few days at a time for as long as he could remember. They were never severe enough to be incapacitating and he was never confined to bed. He was hospitalized for laryngitis in December 1945 and for nasopharyngitis in February 1946.

**Present Illness.** The patient entered the hospital on 5 March 1946 with a history of pain in the left groin which began the preceding evening. This was followed by cramplike pains over the lower back and abdomen.

**Physical Examination.** On admission, he appeared acutely ill with flushed face. There was acute suprapubic pain radiating toward the left lower quadrant and tenderness with some voluntary muscle spasm. Tenderness was also present in the right lower quadrant but not as severe as on the left side. The heart was slightly enlarged to the left and presented a blowing systolic murmur localized at the apex. Blood pressure was 112/65, pulse 100, and oral temperature 100° F.

**Laboratory Status.** A white count on admission revealed 23,300 cells with 75 per cent neutrophils. The urinalysis was negative. The white cell count dropped to 10,000 during the next few days. Sedimentation rate on 1 April was 28 mm. per hour. Blood culture taken on 4 April was sterile after ten days' incubation. Sedimentation rate on 18 April dropped slightly to 22 mm. per hour. On 12 March, a routine chest film showed a slight increase in the markings of both bases, but no specific parenchymal pathology was seen. Although a low-grade temperature ranging between 100 and 100.8° F. persisted from the time of admission, it suddenly rose to 102.4° F. on 17 March. The white cell count became elevated to 23,600 with 85 per cent neutrophils. The sedimentation rate rose to 30 mm. per hour and the urine revealed two plus albumin. Following intensive salicylate therapy, the white cell count dropped again to 11,600 with 87 per cent neutrophils and the pneumonitis and temperature subsided within two days. Chest film on 18 March showed increased markings with small areas of soft infiltrations throughout both lower lung fields which had the typical appearance of rheumatic pneumonia. The following day a chest film showed a

marked diminution in extent and intensity of these infiltrations although the perivascular markings were still increased throughout both lung fields. (Fig. 1.) On 18, 25, and 27 March electrocardiograms were negative except for sinus tachycardia. Throat culture on 23 March revealed nonhemolytic streptococci.

**Clinical Course.** An admission diagnosis of appendicitis was made and the appendix was removed. There was no suppuration, but hyperemia and edema of the appendix were present. (Fig. 2.) A small amount of clear fluid was visible in the lower abdomen. The patient had a rather stormy postoperative course for three days with temperature rise to 101° F. On 16 March the fever recurred and he complained of joint pains with definite swelling and tenderness of the left ankle. Patient became afebrile and asymptomatic after 48 hours of intensive sodium salicylate therapy (40 grains four times daily). The apical systolic murmur disappeared completely. The patient remained afebrile and asymptomatic for about one month but again developed a slightly elevated temperature and sedimentation rate which subsided in one week following intensive salicylate therapy.

### RHEUMATIC FEVER WITH GLOMERULONEPHRITIS

Great variation is noted in the literature concerning the frequency of kidney involvement in rheumatic fever. Gray et al.<sup>17</sup> reported the presence of acute nephritis in 10 to 20 per cent of their cases of rheumatic fever and Bell<sup>18</sup> noted its occurrence in one-fourth of 104 necropsies of rheumatic fever. However, the majority of investigators report a low incidence ranging from zero and 0.67 per cent to 7 per cent. Rolly<sup>19</sup> discovered 16 instances in 2,652 cases (0.67 per cent). Libman<sup>20</sup> and Goldring and Wyckoff<sup>21</sup> found none in their series of 235 deaths due to rheumatic heart disease (118 of which occurred during the acute stage). Baehr and Schiffrin<sup>22</sup> identified three cases of glomerulonephritis, of which only one was definitely concurrent with the fatal attack. In his experience, Fishberg<sup>23</sup> found typical lesions in only two patients. In a study of 3,000 autopsies, Hutton and Brown<sup>24</sup> discovered three cases showing focal glomerulitis and one case with diffuse obliterative renal vascular disease, active rheumatic heart disease and Aschoff bodies in the myocardium. In the foreign literature,<sup>25-28</sup> renal lesions have been described preceding, co-existing or following rheumatic fever manifestations. These were usually focal embolic or acute diffuse glomerulonephritis.

It is difficult to avoid the inference that "rheumatic glomerulonephritis" like "rheumatic pneumonia" exists. Hence, for the first attack of glomerulonephritis occurring during an acute attack of rheumatic fever, it is suggested that the term "rheumatic glomerulonephritis" be employed. It is also possible to have an exacerbation of a previous glomerulonephritis since

even minute quantities of streptococcus toxin may produce a violent allergic reaction.<sup>29</sup> The glomerulonephritis of scarlet fever is precipitated not at the height of infection but during the period of convalescence when sensitization to the streptococcus occurs. There is every reason to assume that this condition is paralleled during rheumatic fever. The lesion is essentially a disturbance of the capillaries of the kidneys similar to capillary involvement elsewhere throughout the body.



FIG. 2. Rheumatic involvement of appendix with edema and slight fibrin deposit of media and serosa, with slight infiltration of lymphocytes and an occasional giant cell (a). Hyperemia of blood vessel (b) and dilation of lymph spaces (c). No evidence of suppuration.

Both of the following cases developed evidences of glomerulonephritis during the course of acute rheumatic fever. The first case is most interesting in that he gave a history of uncomplicated scarlet fever in childhood and a second attack at 18 years which precipitated a kidney exacerbation lasting five months. The sequence of involvement during his hospitalization was scarlet fever, glomerulonephritis, acute rheumatic fever and endocarditis of the mitral valve. It is difficult to state with any degree of accuracy in these cases the exact relationship of the kidney involvement to rheumatic fever, since mild attacks of rheumatic fever are so easily overlooked during childhood.

**CASE 2.** A white male of 18 years, with one month of military service, entered with an upper respiratory infection.

**Antecedent History.** Measles, mumps, chicken pox, whooping cough and scarlatina occurred during childhood

without known complications. One and one half years ago, he had a three-day period of gross hematuria which cleared spontaneously. He was entirely asymptomatic without colic, pain, burning, frequency or nocturia.

**Family History:** Father had rheumatism and one brother died of unexplained convulsions at the age of two.

**Present Illness.** On 12 January 1946 the patient had an upper respiratory infection with sore throat, headache and fever for two days. Two days later a fine nonpruritic rash was noted all over the body.

**Physical Examination.** Temperature on admission was 101° F. Skin showed a fine macular erythematous rash over the face, trunk and extremities which was typical of scarlatina. Pharynx was injected with enlarged tonsils and there was a "strawberry" tongue. Examination was otherwise negative.

**Laboratory Status.** The admission urine showed three plus albumin, numerous red blood cells and positive benzenedene test for blood. The white cell count on admission was 25,950 with 81 per cent neutrophils, 17 per cent lymphocytes and 2 per cent eosinophils. Spinal fluid protein and sugar were normal with a count of three lymphocytes per cu.mm. Sedimentation rate on 15 January was 30 mm. in one hour. On 18 January the white cell count dropped to 11,050 with a normal differential. Daily urinalyses showed a gradual decrease of the albumin and red cells until they became entirely negative on 21 January. On 23 January a trace of albumin was again present. On 26 January occasional red cells were noted again but on 4 February numerous red cells reappeared. A few granular and hyaline casts were present on 8 February. Red blood cell casts were noted five days later. Urine concentration test was normal on 18 February. The urine remained clear from 28 February until 6 March, when occasional red blood cells and granular casts reappeared. The urine reverted to normal until 18 March. One plus albumin with granular casts and red blood cells were again noted but afterward the urine remained entirely clear. The Kahn test was negative. Smears on 28 February and

1 March were negative for malaria parasites. Red cell fragility test was within the upper limits of normal on 8 March. Serum protein and albumin-globulin ratio were normal on 20 March. Sedimentation rates remained persistently elevated between 20 and 30 mm. per hour. A red cell fragility test repeated on 27 March was normal.

**Clinical Course.** Patient appeared acutely ill on admission with a febrile course which lasted until 20 January. Penicillin therapy (20,000 units every three hours) was instituted at once and continued for ten days. On 17 January he was given a transfusion of 200 cc. whole blood. The rash lasted five days but because of continued elevated sedimentation rates, he was confined to bed. On 14 April his left knee suddenly became painful, swollen and hot. The remainder of the examination was negative except for sinus tachycardia. He was placed on large doses of sodium salicylate (40 grains every four hours) and within 24 hours the knee returned to normal. There was a marked elevation in the sedimentation rate. The electrocardiogram appeared normal except for sinus tachycardia. Examination on 18 April revealed a rough blowing systolic murmur at the apex that was transmitted toward the axilla. The murmur became pronounced and was present at the time of discharge.

**CASE 3.** A while male of 18 years, with one month of military service, entered with pain in both knees.

**Antecedent History.** Family history was noncontributory. Past history revealed albuminuria at the ages of 14 and 18 but the urine was negative at the time of his induction. There was no history of kidney disease, scarlet fever or other childhood diseases. Rheumatic history was negative.

**Present Illness.** On 8 January 1946 the patient had a sudden onset of pain in both knees. The pain moved to the right shoulder and hips and, to a lesser degree, the wrists and fingers. Pain in the left knee lasted about three days and in the right knee for one week.

**Physical Examination.** The blood pressure was 118/72. Heart revealed no enlargements.  $P_2$  was greater than  $A_2$ . A loud systolic blow over the pulmonic area proved to be functional in character. Heart tones were slightly distant. No friction rubs or thrills were heard and there was regular sinus rhythm. There was slight enlargement of the epitrochlear, axillary and inguinal lymph glands. They were nontender and discrete.

**Laboratory Status.** Urines were repeatedly negative at the onset except for one-plus albumin on a single occasion. Subsequently, small numbers of red cells began to appear but never amounted to more than five per high power field. No casts were noted. Agglutination test for undulant fever and the heterophile antibody test were both negative. An initial sedimentation rate of 30 mm. per hour dropped to 18 mm. per hour following two weeks of salicylate therapy. Early electrocardiograms showed a second degree A-V conduction delay (PR interval 0.28 second), but this reverted to normal in one month. (Fig. 3.) Blood counts revealed a slight leukocytosis ranging between 13,000 and 15,000 white cells with an essentially normal differential count. Wassermann was negative.

**Clinical Course.** Patient showed an excellent response to sodium salicylate therapy (40 grains four times daily) and the joint pains and temperature rapidly subsided. However, on 7 and 10 February a few red cells were noted in the urine suggestive of a low-grade acute glomerulo-

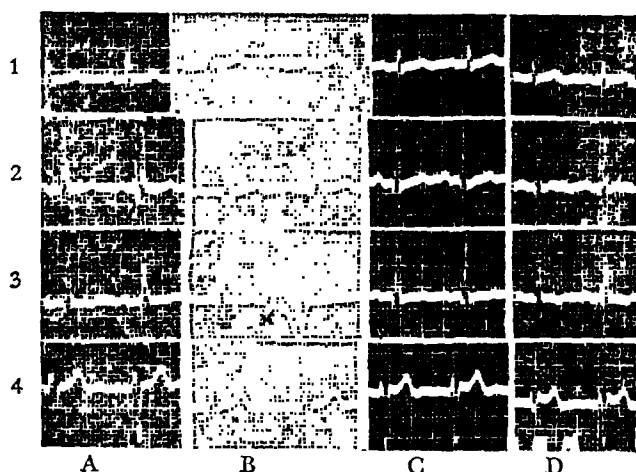


FIG. 3. A. (28 Jan.) First degree A-V conduction delay. PR interval 0.22 second. B. (1 Feb.) Increased A-V conduction delay to 0.28 second with frequent ventricular premature contractions. C. (12 Feb.) Appearance of the electrocardiogram approaches normal. D. Negativity of T waves in leads 2 and 3 appear as evidence of myocardial damage.

nephritis. Occasional red cells persisted for about one month. The blood pressure did not become elevated. The sedimentation rate became normal two months following the onset of his illness. Final diagnosis was acute rheumatic fever with low-grade glomerulonephritis.

### ATYPICAL JOINT INVOLVEMENT

The usual frequency of rheumatic joint involvement is as follows: knees, ankles, shoulders and wrists, and less frequently, the hips, elbows and small joints of the hands and feet. It is rare to have monoarticular pain at the onset and the larger joints are usually involved symmetrically.

In the southwest it has not been unusual to find very mild atypical arthritic manifestations, on occasion, so slight as not to be mentioned by the patient. Frequently, a single atypical joint such as the ankle or wrist, has been involved. Such cases cause considerable difficulty in establishing an early diagnosis. Following a long hike or heavy work, they were frequently diagnosed and treated as sprains. A previous rheumatic history, cardiac involvement, persistent low-grade temperature, elevated sedimentation rate and the clinical course aided in establishing the correct diagnosis. It is important to carefully investigate the occurrence of atypical joint involvement to avoid making erroneous diagnoses such as sprain, strain, "lumbago," and early infectious or traumatic arthritis. It is well to remember that joints more subject to stress and strain are usually involved first in rheumatic fever.

### RHEUMATIC ARTHRITIS RESEMBLING "SPRAINED ANKLE"

A definite history of injury to the ankle, physical findings of tenderness and swelling with no previous rheumatic history, made the admission diagnosis of acute ankle sprain seem plausible in the following case. Yet the subsequent flitting joint pains, elevated white cell count and sedimentation rate, and response to salicylates, were necessary to establish the correct diagnosis of acute rheumatic fever.

**CASE 4.** A white male of 19 years, with four months of military service, entered with a "sprained ankle." He had pneumonia a number of times in the past. No rheumatic history was obtainable. He suffered a fractured right clavicle in 1940 and a fractured pelvis in 1935. Family history was noncontributory.

**Present Illness.** On 1 April 1945 while alighting from a truck, the patient stepped on a rock and "twisted his ankle" while engaged in a field problem. He was able to continue with his outfit and did not feel much discomfort until five hours later. He then noticed pain and swelling but no discoloration. He was referred to the hospital for a "sprained ankle" and local treatment was instituted. His left knee became swollen but not painful the following day. This was followed in two days by a painless swelling of the right knee. His hands also swelled and became very painful.

**Physical examination** was entirely negative except for the joints. Both knees were slightly swollen, tender and very painful on motion. Heart examination was entirely negative.

**Laboratory Status.** Electrocardiogram revealed a sinus tachycardia with rate of 102 and PR interval of 0.16 second and was otherwise normal. Sedimentation rate was 34 mm. per hour on admission but dropped to 27 mm. per hour on 9 April. Urinalysis was essentially negative. On admission, the white cell count was 11,700 and the hemoglobin was 97 per cent.

**Clinical Course.** Patient showed excellent improvement with salicylates (40 grains every four hours), the joints subsiding completely within one week. The final diagnosis was acute rheumatic fever with polyarthritis.

### MONOARTICULAR INVOLVEMENT OF ATYPICAL SMALL JOINTS (ASTRAGULUS)

**CASE 5.** A white male aged 19, with two months of military service, was admitted with pain in his left foot.

**Antecedent History.** His father had rheumatism and was unable to work for the past year.

**Personal History:** Acute follicular tonsillitis occurred on 5 April 1943 and measles on 28 March 1943. He gave a history of "acute rheumatism" at the age of seven with swelling of both knees. He was in bed for two weeks but was incapacitated for a long time following this attack.

**Present Illness.** He was discharged from this hospital 21 April 1943 following an attack of acute follicular tonsillitis. After returning to strenuous exercises he began having pain and tenderness in his left foot in the region of the astragalus. He was awakened in the early morning of 26 April with increasingly severe pain in his foot and was admitted to the hospital.

**Physical Examination.** Heart rate was 96, blood pressure 110/70, no cardiac enlargement was present and no murmurs were heard. There was marked tenderness sharply localized over the astragalus bone of the left foot. Remainder of the examination was normal.

**Laboratory Findings.** On 20 April 1943, the white blood count was 22,800 with neutrophils 79 per cent, lymphocytes 17 per cent, eosinophils 3 per cent, monocytes 1 per cent; hemoglobin 90 per cent; Kahn test and urinalysis were negative.

27 April—Sedimentation rate 23 mm. in 15 minutes, 30 mm. in one hour.

2 May—Sedimentation rate 12 mm. in 15 minutes, 27 mm. in one hour.

7 May—No hemolytic streptococci found in throat smear.

7 June—Sedimentation rate 5 mm. in 15 minutes, 14 mm. in one hour.

2 July—Sedimentation rate 2 mm. in 15 minutes, 12 mm. in one hour. Urinalysis negative.

12 July—Sedimentation rate 0.5 mm. in 15 minutes, 5 mm. in one hour.

Electrocardiogram on 3 May revealed a rate of 72, PR interval 0.12 second and the complexes were normal with sinus arrhythmia. On 31 May the rate was 76, PR interval 0.18 second, and the complexes were normal with regular sinus rhythm.

**Course.** On admission, the left foot was tender to pressure over the astragalus and slight localized swelling was



noted. Two carious teeth were extracted on 23 May. The pain in the left foot gradually subsided. The patient had been on sulfonamide therapy but salicylates were substituted. No cardiac murmurs were audible at this time. On 29 May the knees and left ankle became slightly stiff and painful. The sedimentation rate was 15 mm. per hour. A soft systolic murmur appeared at the apex and a soft blowing diastolic was brought out over the aortic areas after exercise. On 12 June the diastolic murmur persisted over the left sternal margin at the third and fourth intercostal spaces. The painful joints finally cleared up and he was maintained at complete bed rest for two additional weeks. The sedimentation rate became normal after one month. The final diagnosis was recurrent rheumatic fever with polyarthritis and aortic insufficiency.

#### RHEUMATIC FEVER INVOLVING SACRO-ILIAC JOINTS

This case presents an interesting phenomenon of acute rheumatic fever. At first, the atypical joint involvement suggested sacro-iliac pain due either to rheumatoid arthritis or referred back pain from an ovarian cyst. However, the smoldering character of this attack of rheumatic fever was exacerbated on the third postoperative day following an ovariectomy and appendectomy. The development of polyarthritis and excellent therapeutic response finally established the correct diagnosis. Subsequently, a history of repeated attacks of polyarthritis during childhood was obtained.

**CASE 6.** A white female, aged 24, with one year of military service, entered with pains in lower back and abdomen.

*Antecedent History.* Measles, mumps, chickenpox, and whooping cough occurred during childhood. Polyarthritis was present at the age of nine necessitating bed rest for three weeks. Two mild attacks of polyarthritis recurred since that time.

*Family History:* Father died of pneumonia and mother died of a heart attack. Patient was five years old at the time she was adopted.

*Present Illness.* The patient was admitted to the hospital on 30 March 1946 with a chief complaint of backache and low abdominal pain.

*Physical examination* was not remarkable except for complaints of very low abdominal tenderness, bilateral sacro-iliac pain with tenderness over the right sacro-iliac joint. Blood pressure was 110/70. No cardiac enlargement or murmurs were present.

*Laboratory Status.* Repeated studies of the blood and urine were within normal limits. Sedimentation rate was 102 mm. per hour on 1 April, 30 mm. per hour on 9 April, 24 mm. per hour on 13 April, and 8 mm. per hour on 17 May. X-rays of the spine and sacro-iliac joints revealed no evidence of arthritis.

*Clinical Course.* Patient continued to complain of low abdominal tenderness and bilateral sacro-iliac pain. On 23 April 1946 an appendectomy was performed and a cyst was removed from the left ovary. On the third postoperative day there was a sudden onset of pain, heat, redness and swelling of the right hip, both knees and left elbow. On examination, the joints were red, hot and markedly tender. Temperature rose to 102° F. with a pulse rate of 120.

Salicylate therapy (40 grains every four hours) was instituted. Patient responded well but developed mild symptoms of salicylate intoxication necessitating decreased dosage. Throughout her clinical course numerous electrocardiograms were entirely normal. Chest x-rays, flat plates of the abdomen and intravenous pyelograms were normal. Physical examination on 20 May was entirely within normal limits. There was no cardiac enlargement and no murmurs could be elicited. A subsequent flare-up of joint pains prolonged her hospitalization for an additional month. The final diagnosis was acute rheumatic fever.

#### CASE OF REITER'S DISEASE WITH OLD RHEUMATIC HEART DISEASE

On another occasion, Gersh and the author<sup>30</sup> presented a study of Reiter's disease. The following case of Reiter's disease presented a definite past history of rheumatic fever. The occurrence of gonorrhea followed by arthritis 16 months before the present admission with the typical triad of Reiter's disease make this case an unusual diagnostic problem. Gonorrheal arthritis was ruled out by the clinical course; absence of the gonococcus in smears and cultures from the eyes, urethra, prostate and joints; repeated presence of a hemolytic staphylococcus albus in smears and cultures from the eyes, joint fluid, urethra and prostate; the prolonged course with numerous remissions and exacerbations; and lack of response to sulfonamides and penicillin.

Reiter's<sup>31</sup> disease is a rare syndrome characterized by a triad of arthritis, urethritis and conjunctivitis. Hence it may first attract the attention of the internist, ophthalmologist or urologist. Bauer and Engleman<sup>32</sup> found recurrences in about one-fourth of the cases which may involve any or all of the three systems and persist from one to five months. Colby's<sup>33</sup> studies showed that renal complications, such as hydro-nephrosis, may occur. Although many organisms and allergy have been advanced as the etiologic agent, none has been definitely established. Our present and past investigations<sup>30</sup> suggest the presence of a staphylococcus. These cases do not respond to the sulfonamides or penicillin. There is no known relationship to either rheumatic fever or gonorrhea.

**CASE 7.** A white male, aged 23, with three months of military service, entered with swelling of the left knee.

*Antecedent History.* Family history was entirely negative except for his mother who died of pneumonia at the age of 40. Patient had no operations or injuries but had one attack of gonorrhea 16 months prior to admission.

*Present Illness.* Patient had "rheumatism" which had involved the knees at the age of three. He had had minor attacks since then at infrequent intervals. On several occasions they necessitated leaving school for a few days at a time. He was not told of any murmurs and he gave no history of chorea, frequent severe sore throats, severe headaches, nose bleeds, growing pains, scarlet fever or cardio-

vascular-renal disease. His last severe attack occurred in 1939 when he was incapacitated for nine months with acute rheumatic fever and heart disease but there was no joint involvement. About 16 months ago he acquired gonorrhea. Five days later the right knee became swollen and red. It required daily aspiration for an entire month. The fluid was thick and yellow. Short-wave diathermy and sulfa drugs finally cleared it up. He thought his "right knee has never been quite the same since then."

**Physical Examination.** There was slight engorgement of the pharynx. Blood pressure was 110/78. Heart revealed no enlargements.  $A_2$  was greater than  $P_2$  and there was regular sinus rhythm. There was a very faint systolic murmur at the apex heard in the horizontal position but it was not transmitted. The heart sounds were of good myocardial quality. The left knee joint contained a moderate amount of fluid. There was no redness or tenderness and no other joints were involved. Prostatic examination revealed a moderate diffuse enlargement.

**Laboratory Status.** X-rays of the right knee on two occasions showed slight sharpening of the superior and inferior margins of the articular surface of the patella but were otherwise negative. Lung fields, heart and great vessels appeared normal. Serial electrocardiograms presented slight sinus arrhythmia with a rate around 74 and PR interval of 0.18 second. Urinalysis showed a specific gravity of 1.007 with six plus cells per high power field. Prostatic smears revealed masses of pus cells but no specific organisms were identified. The white cell count was 13,558 with 64 per cent neutrophils, 34 per cent lymphocytes and 2 per cent eosinophils. The red cell count was 6,100,000 with 100 per cent hemoglobin. Sedimentation rate on admission was 12 mm. in one hour. A small amount of fluid was aspirated from the right knee on 26 January 1945 and revealed 6,400 cells with 60 per cent neutrophils and 40 per cent lymphocytes, specific gravity 1.006, two plus trichloroacetic acid test, and no organisms on direct smear. Because of the purulent discharge from the conjunctiva, a culture was performed which revealed hemolytic staphylococcus albus. Sedimentation rates taken at frequent intervals never rose above 12 mm. in one hour. Dark field examinations of a tiny ulceration of the penis were negative for *Treponema pallidum*, and the Frei test was negative. It healed rapidly without treatment and was considered to be of traumatic origin. The Kahn test was negative. Temperature, pulse and respirations were normal throughout. On 2 April about 30 cc. of clear slightly orange-colored fluid was removed from the right knee which had again become swollen. This revealed a specific gravity of 1.006, a white count of 15,600 cells with 84 per cent polys and 16 per cent lymphocytes and remained sterile after five days culture. Another knee tap performed three days later revealed 4,000 white cells with 82 per cent polys and 18 per cent lymphocytes, specific gravity 1.010, trichloroacetic acid four plus and smear and culture revealed no pathogenic organisms. The urethral discharge appeared on 2 April. Culture revealed a nonhemolytic *Staphylococcus albus* from both urethra and prostate. No spirochetes<sup>31</sup> or gonococci were isolated on smear, culture or dark field examinations.

**Clinical Course.** Because the patient had a slight purulent discharge from the conjunctiva for three weeks prior to admission, eye consultation was requested. Boric acid eyedrops were prescribed for chronic catarrhal conjunctivitis. Vision was 20/20 bilaterally and the patient was

found to be moderately color blind. Eye cultures showed a growth of hemolytic staphylococcus. He progressed satisfactorily except for a slight aching in both knees on prolonged walking and slight residual weakness. Following a march on 3 March, definite knee swelling reappeared and he was hospitalized again. Ten cc. clear fluid were removed. Urethral smears and cultures again revealed non-hemolytic *Staphylococcus albus*. Dark field examinations of knee fluid and urethral discharge were negative for spirochetes. A second culture of urethral discharge on 30 March demonstrated hemolytic *Staphylococcus albus*. Urine samples were repeatedly negative. A second culture of the eyes revealed nonhemolytic *Staphylococcus albus*. The patient developed pain and stiffness of the cervical spine for one week during a period of inclement weather. X-rays of the cervical spine and sedimentation rate were found to be negative. Following a course of massages, the prostate finally became normal on 31 March. On 6 April there was a recrudescence of mild conjunctivitis which responded rapidly to zinc drops. On 16 April a small amount of fluid reaccumulated in the right knee. Because of the numerous exacerbations which are so typical of Reiter's disease, the patient was transferred to a General Hospital for further treatment and disposition.

The occurrence of the typical triad of urethritis, conjunctivitis and arthritis with numerous exacerbations and repeated absence of the gonococcus on smear and cultures from all foci established the diagnosis of Reiter's disease. This case is also unusual because of the past history of rheumatic fever which confused the early picture since there was initial joint involvement. The original gonorrheal infection was questionable in that there was no residual joint immobility despite reaccumulations of fluid requiring daily aspirations over a period of one month. No specific organisms were recovered and there was no residual scarring so frequently encountered with gonorrheal infection of the eyes, especially without the use of specific therapeutic agents.

#### THE RECOGNITION OF MINIMAL INVOLVEMENT OF THE AORTIC VALVE

##### AORTIC INSUFFICIENCY

The recognition and evaluation of early insufficiency of the aortic valve which may develop during an acute attack of rheumatic fever is frequently difficult. The prevention of severe damage may be attainable when the diagnosis can be established sufficiently early. Therefore, proper emphasis on the need for careful cardiac examinations cannot be overstated. "Pure" aortic insufficiency is frequently overlooked during an attack of rheumatic fever. An early "pure" lesion is sometimes difficult to elicit because of the faint high-pitched murmur. The author<sup>34</sup> collected 24 cases of mild aortic insufficiency which had been missed repeatedly in civilian life and in the army.

Disease of the aortic valve is often of very slight degree,<sup>35</sup> but recognition of an incipient active lesion may be greatly benefited with the early usage of massive salicylate dosage.<sup>3</sup> During an acute attack, the

diastolic murmur may be entirely absent, then suddenly appear as a faint blow a few days later, only to become distinct in a week since it is produced by the slightest retraction or distortion of the valve. Stenosis takes a much longer time to develop and eventually may go on to marked calcification.<sup>36</sup> Of the visual aids in cardiac examination,<sup>37, 38</sup> such as electrocardiography, stethography and cardioscopy, the last two are not so extensively enjoyed as to be of practical value.

However, even before the full effects of aortic insufficiency are brought to bear upon the cardiovascular system with confirmatory peripheral signs, the faintest diastolic murmur is manifest by employing the following method of physical diagnosis: (a) the patient exercises by hopping 25 times on each foot, (b) then leans forward moderately in the erect position, (c) during a complete expiration, (d) a diaphragm type of stethoscope is employed, (e) and applied to the third and fourth intercostal spaces just to the left of the sternum and the second intercostal space just to the right of the sternum. Rarely, the murmur heard is best in the horizontal position. A comparison of the intensity of murmur magnification thus elicited will convince the examiner of the value of carefully performing this method of cardiac auscultation. Early murmurs are described as soft, blowing, high-pitched, streaming or faint. In most cases, it radiates downward along the left border of the sternum, and is heard loudest over the third intercostal space just to the left of the sternum.

The following case illustrates the importance of early recognition of insufficiency of the aortic valve developing during an acute attack of rheumatic fever. Continued high dosage of salicylates is indicated after the sedimentation rate and fever approach normal in order to minimize the degree of valvulitis.

**CASE 8.** A white male, aged 30, with seven months of military service, entered with multiple joint pains.

**Antecedent History.** His father died at 72 years from cancer of the stomach. Ten siblings were living and well. He had "rheumatism" with swollen joints of the extremities in 1929 which confined him to bed for two weeks. He was unable to do any work for two months.

**Present Illness.** In September 1929, at the age of 16, he had pain and swelling in the joints of the upper and lower extremities which incapacitated him for around eight weeks. He then remained in good health until the present hospitalization. On 8 April 1943 he acquired a cold during wet weather. The following day he developed pains in the joints of his toes, knees, hips, hands, elbows and shoulders.

**Physical examination** of the heart revealed a blood pressure of 120/70, rate 80, no enlargements and no murmurs were heard. The knees, wrist, and small joints of the hand were slightly swollen, red, warm and painful to motion. Remainder of the examination was normal.

**Laboratory Findings.** On 13 April 1943, the sedimentation rate was 21 mm. in 15 minutes, and 30 mm. in one hour. White cell count was 15,200 with polys 78 per cent and lymphocytes 22 per cent. Red cell count was 4,600,000. The Kahn test was negative. On 3 May sedimentation rate was 15 mm. in 15 minutes, 30 mm. in one hour, white cell count 11,100 with polys 64 per cent and lymphocytes 36 per cent, hemoglobin 81 per cent. On 20 May throat culture revealed no hemolytic streptococci. Urinalysis was normal. White cell count was 8,100; red cell count was 4,380,000 with 74 per cent hemoglobin. June 7: sedimentation rate 6 mm. in 15 minutes, 20 mm. in one hour. White cell count 9,200, hemoglobin 90 per cent. June 21: sedimentation rate 16 mm. in one hour. Urinalysis negative. July 6: sedimentation rate 9 mm. in one hour. EKG on 14 April: rate 82, PR interval 0.18 second, regular sinus rhythm. May 4: EKG shows rate 68, PR interval 0.28 second indicating a second degree A-V conduction delay. May 10: EKG performed 20 minutes after 1/50 grain atropine revealed a rate of 74 and PR interval 0.20 second. June 4: EKG showed a PR interval of 0.20 second. July 1: EKG rate 66 with a PR interval 0.20 second. Interpretation was regular sinus rhythm. X-ray of the chest on 12 July was normal.

**Course.** On admission the knees, wrists and small joints of the hands were acutely inflamed. Temperature was 100° F. Patient was placed on sodium salicylate (40 grains every four hours) but had a slight temperature ranging from 99 to 100° F. for the following two weeks. The fever fell by lysis as the joint symptoms subsided. During this time the pains migrated to practically every joint of the extremities. He remained afebrile after 27 April. As the joint symptoms subsided, he developed a soft, blowing diastolic murmur heard best in the third left intercostal space with slight radiation down the left parasternal border. This murmur persisted but could not be elicited without the recommended procedure. The final diagnosis was acute rheumatic fever with mild aortic insufficiency.

#### AORTIC STENOSIS

Although the murmur of aortic insufficiency is frequently missed, the diagnosis of aortic stenosis is made too frequently when any basal systolic murmur is elicited.

A systolic murmur at the aortic area may be produced by aortic stenosis of rheumatic origin and dilatation of the aorta with or without aneurysm due to syphilis, hypertension or arteriosclerosis. Less frequently, dissecting aneurysm,<sup>39</sup> calcific aortic valve stenosis,<sup>36</sup> or congenital lesions (congenital subaortic stenosis or bicuspid valve) may be at fault. Transmission of systolic murmurs from any area of the heart, especially pulmonic, may give rise to difficulty.

Although a well-developed murmur with or without corroborative findings is comparatively simple to diagnose, the early recognition of minimal involvement may cause some difficulty. It is generally soft and blowing in character with slight or no transmission upward. The duration is variable but usually extends throughout systole with a tendency toward the

diminution of the second sound. It is best elicited with the routine suggested above for the search of an aortic insufficiency. The exercise test tends to rule out transmitted functional murmurs which diminish in intensity. It may also bring out an accompanying thrill and symptoms (angina, dyspnea, syncope).

The following case illustrates the importance of careful examination in the detection of minimal aortic stenosis developing during an attack of acute rheumatic fever. Salicylate therapy in large doses is indicated over a long enough period following subsidence of joint symptoms to prevent the development of carditis; and if already present, to minimize the damage.<sup>3</sup> The premature discontinuation of salicylates in this case resulted in recrudescences with development of a well-defined stenotic lesion and evidences of myocardial damage. The murmur was elicited only after repeated examination of the aortic areas. A case of "pure" aortic stenosis was selected for presentation to avoid the possible confusion in diagnosis when other murmurs are present.

**CASE 9.** A white male, aged 20, with nine months of military service, was admitted with generalized weakness.

**Present Illness.** He entered the hospital on 30 March 1946 with a chief complaint of generalized weakness for three days and tachycardia, occasional cough and a sensation of tightness in his chest. There was slight soreness of the throat and aching of the bones and muscles.

**Physical examination** showed only a mildly injected pharynx and postnasal discharge. The initial impression was that of acute nasopharyngitis.

**Laboratory Status.** Red cell count was 4,300,000, white cell count 7,600 with a differential count of 64 per cent polys and 36 per cent lymphocytes. Heterophile antibody titer was negative. Sedimentation rate was 30 mm. per hour.

**Clinical Course.** The patient continued to complain of soreness in his knees and elbows. Repeated smears of his blood showed no atypical type III lymphocytes. On April 25 rheumatic fever was first suggested as a possible diagnosis and sodium salicylate (20 grains four times daily) was instituted with excellent response. By 3 May the sedimentation rate was within normal range and the salicylates were discontinued.

After repeated examinations a fairly loud rough systolic murmur was heard best over the precordium but loudest at the aortic and pulmonic areas. No diastolic component was heard. Three days after discontinuation of the salicylates the patient again began to complain of pain and aches in his shoulders which progressed to the wrists and ankles. The sedimentation rate again rose to 26 mm. per hour. He had a persistent tachycardia ranging from 112 to 120. On 21 May the sedimentation rate rose to 32 mm. per hour and EKG showed a first degree heart block. (Fig. 4.) No murmurs or friction rubs were heard at this time. Because of the exacerbation, salicylate therapy was again instituted. The patient soon became asymptomatic, but on 4 June a very faint, localized systolic blow was heard at the first aortic area with the recommended method of examination. By 8 June the sedimentation rate was again down to 15 mm. per hour and on 11 June the sedi-

mentation rate dropped to 11 mm. per hour. On 13 June the patient complained of dyspnea and a feeling of weakness. His heart beat rapidly when he exerted himself. Physical examination showed a pulse of 120 and respirations of 22. Lungs were clear to percussion and auscultation. A definite loud systolic murmur was audible at the aortic area. The sedimentation rate and fever completely subsided two and a half months after admission. Comparative EKG studies at this time revealed definite changes suggestive of myocardial damage. Final diagnosis was acute rheumatic fever with aortic stenosis.

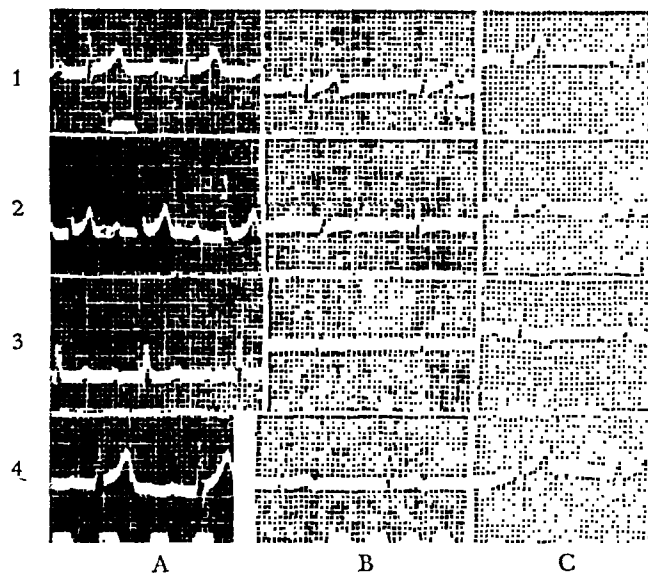


FIG. 4. A. (17 May.) First degree A-V conduction delay. PR interval 0.26 second. T waves upright. Slight elevation of ST complexes in standard leads. B. (6 July.) Decreased voltage with slurring of QRS complexes and decreased voltage with diphasic T waves suggestive of myocardial damage. C. (12 July.) Normal appearance at the time of recovery.

## RHEUMATOID ARTHRITIS AND RHEUMATIC FEVER

Certain similarities serve to confuse rheumatic fever and rheumatoid arthritis.<sup>40</sup> Both have a tendency to occur in families living in the temperate zones and may be preceded by upper respiratory infections. The similarity of the subcutaneous nodules and the possible etiologic role of a hemolytic streptococcus is common to both.

Bayles,<sup>41</sup> Baggenstoss and Rosenberg,<sup>42, 43, 44</sup> and Conrad<sup>45</sup> found marked similarities in studies totaling 108 necropsies. On the other hand, Bennett's autopsy studies<sup>46</sup> revealed differences. More than one-third of the patients with rheumatoid arthritis show evidence of rheumatic heart disease by clinical examination. This suggests that they may bear some relationship. However, since the exact etiology of either disease has not been established, most authorities feel it is futile to speculate on the exact relationship at present.

Hench<sup>47</sup> suggested that clinicians may be missing associated lesions of rheumatic carditis in patients with rheumatoid arthritis. Masters et al.<sup>48</sup> carefully questioned patients with rheumatoid arthritis and found a history of coincidental rheumatic fever in 11 per cent. There are definite clinical and laboratory differences which may enable a differentiation. In infectious arthritis, the joints are usually involved as follows; knees, fingers, shoulders, wrists, ankles, elbows, spine and ultimately practically every joint in the body. In rheumatic fever the joints are ordinarily involved as follows: knees, ankles, shoulders and wrists and less frequently hips, elbows and small joints of the hands and feet. It is further differentiated from arthritis by the infrequent involvement of smaller joints, much less muscle wasting and rare skin changes (vascular and thermal).

Rheumatic fever first occurs under 15 years of age in 90 per cent of the cases, almost never results in permanent joint damage, and may also involve lungs and pleura. Rheumatoid arthritis begins after 15 years of age in more than 90 per cent of the cases, very frequently results in permanent joint damage but never affects the lungs and pleura. The response to salicylates is dramatic in the former and gives only temporary and slight relief in the latter. EKG changes are present in about one-fourth of the rheumatic fever cases. The antistreptolysin titer is increased in rheumatic fever and normal in rheumatoid arthritis. X-rays are positive later in rheumatoid arthritis and usually negative in rheumatic fever.

It is a well known fact that pain, stiffness and other symptoms may precede any roentgen changes by months or years.<sup>49</sup> Vontz<sup>49a</sup> suggests that inasmuch as several years may elapse before characteristic roentgen changes are demonstrable, the diagnosis of rheumatoid arthritis in the early stages should be made on clinical evidence alone.

In the following illustrative case, the family history, severe and frequent joint involvement, atypical joint pains (terminal phalangeal joint and spine) and low white count strongly suggested a diagnosis of rheumatoid arthritis. This impression was strong enough to indicate the use of gold injections and other medications in civilian life. However, the flitting nature of the joint pains, cardiac findings and therapeutic test with salicylates established the diagnosis as rheumatic fever.

CASE 10. A white male, aged 27, with four months of military service, was referred for chronic joint difficulties.

*Antecedent History.* His father had rheumatism for many years and one brother died of pneumonia. He had the usual childhood diseases and thought that he had scarlet fever during childhood. At the age of seven he had

painful knees aggravated by exercise and was told it was due to "growing pains." This was present intermittently until the age of 11 when he was finally put to bed. From then until about three years ago he averaged approximately one severe episode annually that required bed treatment. During the past year his attacks became more frequent. He had an appendectomy at the age of 12 and gonorrhea six years ago requiring treatment for six months.

*Present Illness.* In the past two years, he had about four severe attacks of joint trouble requiring up to two months in bed. He was in the service four months and participated in all training activities until this hospitalization. The present attack started one week previously when he awoke to find his left knee swollen and very sore. His left ankle was also sore but not swollen and he was unable to walk for a few days. These joints improved but the right wrist became very sore and swollen. His back felt somewhat stiff but no other joints were involved except the right index finger. The present attack was most severe. There was no history of cardiac involvement, recent colds or acute illnesses. In the past his arthritic manifestations were treated with gold injections and various medications for rheumatoid arthritis.

*Physical examination* revealed a heart rate of 100, regular rhythm and no enlargements.  $P_2$  equalled  $A_2$  and was accentuated on exercise. There was a faint systolic murmur over the precordium, loudest at the apex and more pronounced after exercise. Blood pressure was 122/70. Abdomen revealed an old appendectomy scar. There was considerable swelling of the right wrist with marked limitation of motion but no heat or redness. The terminal joint of the right index finger was painful on motion but not swollen or red.

*Laboratory Status.* EKG was normal. Urinalysis revealed one plus albumin, and three pus cells per high power field. Sedimentation rate was 25 mm. in one hour, 7,200 white cells per cu.mm. were present with 61 per cent polymorphonuclear cells and 39 per cent lymphocytes, and the hemoglobin was 84 per cent.

*Clinical Course.* Patient showed rapid improvement with salicylates (40 grains every four hours). The final diagnosis was acute rheumatic fever.

#### EPIPHYSITIS (SCHEUERMANN'S DISEASE) AND RHEUMATIC FEVER

The following case is of interest because of the occurrence of symptomatic epiphysitis in a female with a definite rheumatic history and valvular heart disease. A recrudescence of rheumatic fever was ruled out by the involvement of the spine, manifested by x-ray changes (Fig. 5), constant pain and stiffness with secondary root involvement in the form of a burning girdle pains, and absent temperature.

CASE 11. A white female, aged 36, with two and a half years of military service, was admitted with low back and subcostal pains.

*Antecedent History.* She had the usual childhood diseases with no complications. She had chorea at the age of nine which required treatment for six months. She was told she had a heart murmur at the age of 19 and again on induction into the army.

*Present Illness.* She had sharp burning pain under both

rib margins and pain in the lower back for three weeks. The pain was constant and awakened her early each morning. It was aggravated by movement and was associated with stiffness on arising or after prolonged sitting. There was no history of back injury or strain, chills or fever and no genito-urinary symptoms. In 1939 she had a similar mild attack of rib margin pain which lasted about two days, and another in 1942 which persisted for one week.

*Physical examination* revealed a well-developed and well-nourished female who appeared acutely ill. She held her trunk rigidly when sitting and had difficulty in bending forward or laterally. The upper teeth were absent. Blood pressure was 108/60. There was slight enlargement of the heart and occasional extrasystoles were present.  $P_2$  was not accentuated. In the lateral recumbent position an apical rumbling presystolic murmur ending in an accentuated first sound and a faint soft blowing systolic murmur were heard. There were no thrills or friction rubs. Heart tones were of good quality. There was tenderness on pressure along both costal margins and over the sacro-iliac joints and the entire spine. There was slight spinal muscular spasm but no atrophy. Reflexes and sensorium were normal.

*Laboratory Status.* Red and white cell counts were normal on several occasions. Urinalysis was negative. Sedimentation rates varied between 25 mm. and 33 mm. per hour. Kahn test was negative. Cervical smears were negative for pathogenic organisms. A blood culture was sterile. EKG was normal. X-ray studies on 15 June 1945 revealed an enlargement of the transverse cardiac diameter with straightening of the left cardiac border. These findings were consistent with mitral disease. The lumbosacral spine and sacro-iliac and hip joints showed no significant osseous or articular changes on two x-ray examinations. The thoracic spine showed evidence of epiphysitis (Scheuermann's Disease) but there were no x-ray changes of spondylitis. (Fig. 5.)

*Clinical Course.* She was given diathermy to her back daily, sodium salicylate (15 grains four times daily) and thiamine chloride (10 mg. three times daily) for the neuralgia. No improvement was obtained and on 6 July she was started on typhoid injections. She received four intravenous injections without any particular benefit. On 17 July she was started on larger doses of thiamine chloride (50 mg. intramuscularly daily) and gradually improved with the disappearance of all symptoms. Final diagnosis was mitral insufficiency and stenosis due to old rheumatic fever, and epiphysitis of the lower dorsal and lumbosacral spine with secondary intercostal neuralgia.

#### RHEUMATIC FEVER FOLLOWING AN ATYPICAL SOURCE OF INFECTION

The problem of extrarespiratory tract infections in the causation of rheumatic fever has not been adequately studied. "The rheumatic state" is probably the best designation for an individual sensitized by a streptococcus infection to the point where he responds to further absorption of the products of streptococci by constitutional and tissue reactions. From all available information the portal of entry would normally appear to be through the throat and upper respiratory tract and rarely by otitis media and sinusi-

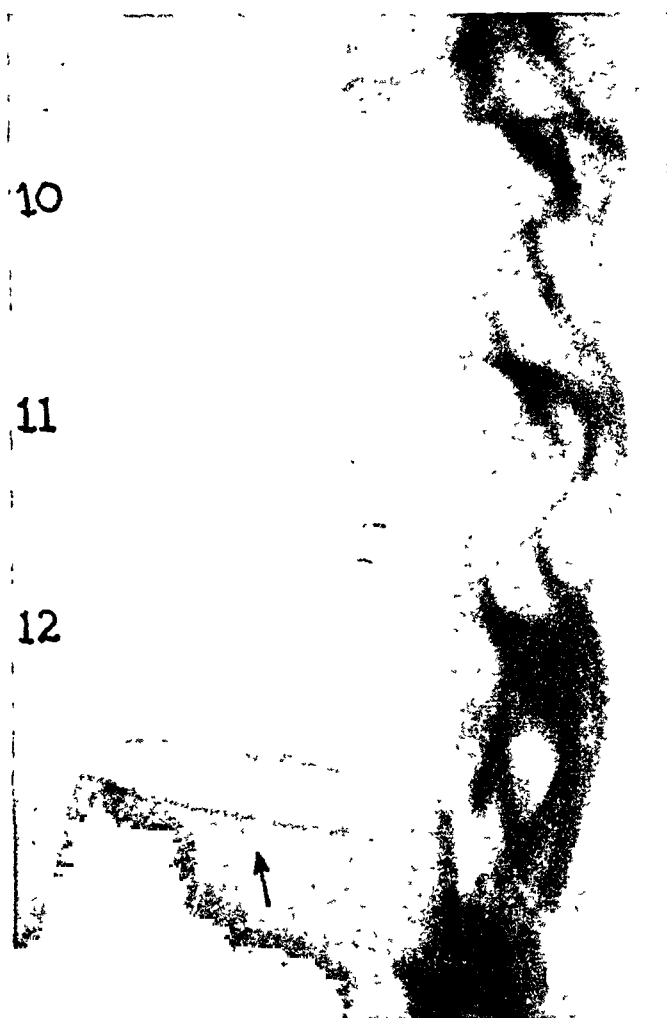


FIG. 5. Epiphysitis (Scheuermann's disease) of 10, 11, 12 dorsal vertebrae with distinct irregularity of vertebral borders and slight wedging. There is a slight resulting kyphosis. Arrow indicates a Schmorl's node. No evidence of spondylitis.

tis. However, there appears to be no good reason why the streptococcus or its products from some atypical focus cannot involve previously sensitized body tissues. Menzer<sup>50</sup> held the view that rheumatic fever may be caused by a variety of organisms, especially streptococci, and that the lymphoid tissues furnish a favorable soil for the development of this infection. The question of a specific type or strain of streptococcus is not within the scope of this paper.

In elevated tropical areas having colder climates, there is a parallel incidence of scarlatina, erysipelas and puerperal fever in the causation of rheumatic fever.<sup>51</sup> Attacks of joint pains may be preceded on very rare occasions by such diverse operations as cholecystectomy and appendectomy or erysipelas following a mastoidectomy.<sup>52</sup> Scarlet fever itself may produce a scarlatinal synovitis which usually appears at the end of ten days and disappears in a week; or more rarely, a suppurative arthritis may occur.

The following case is of unusual interest in that cellulitis of a leg with secondary lymphangitis and lymphadenitis probably precipitated an attack of rheumatic fever. The "soil" for this extrapulmonary tract invasion was prepared five years previously by a definite attack of rheumatic fever. The occurrence of cellulitis with invasion of regional lymphoid tissue several days before a typical attack of rheumatic polyarthritides would seem to indicate that the body tissues previously sensitized to rheumatic infection responded to re-infection from an atypical focus.

**CASE 12.** A white male, aged 18, with three months of military service, entered the hospital with a spreading skin infection of the leg.

*Antecedent history* was entirely negative except for a sprained back at the age of 17, and scarlet fever and measles in childhood without known complications. Venereal diseases were denied. Family history was entirely negative.

*Present Illness.* At the age of 13 the patient was laid up with multiple joint pains for a period of six months, but no known complications ensued. Since that time he had intermittent joint swellings which did not incapacitate him excessively. About two months prior to admission he "skinned" his right knee and subsequently developed a cellulitis with lymphangitis and lymphadenitis of the right inguinal region. Several days later he began to notice pain in the left knee, right shoulder and finger joints. There was no respiratory infection prior to the attack.

*Physical examination* was entirely negative except for the bones and joints which were painful on weight bearing or movement, especially where either knee or the right thumb was involved. There was no evidence of swelling or redness. At the time of transfer from the surgical service, the infection of the right knee had completely subsided with penicillin therapy. Blood pressure was 125/75, regular sinus rhythm, and  $P_2$  equalled  $A_2$ . Heart was not enlarged and tones were of good myocardial quality. A very faint apical systolic murmur was noted intermittently but more recently had disappeared. It never was transmitted and tended to disappear with exercise.

*Laboratory Status.* Numerous electrocardiograms revealed no abnormalities. The PR interval ranged between 0.14 and 0.16 second. X-rays of the right knee presented no changes and the heart size was normal. Urinalysis showed good concentration with no sugar or albumin. White cell count on admission was 6,000 with 68 per cent neutrophils and 32 per cent lymphocytes; red cell count was 4,450,000 with 90 per cent hemoglobin. Sedimentation rates remained between 20 mm. to 26 mm. in one hour.

*Clinical Course.* Patient improved considerably on salicylates but had another flare-up of the left ankle five weeks after admission. This spread to the opposite ankle and the right knee two days later. The temperature and joints readily subsided on salicylates. The differential diagnosis rested between chronic infectious arthritis and rheumatic fever. The latter diagnosis was preferred in view of the history of rheumatic fever at the age of 13, the attacks of multiple flitting joint involvement of a polycyclic nature. In addition, the absence of x-ray findings of the joint and excellent response to salicylates were significant factors in establishing a diagnosis of acute rheumatic fever.

## THE PERMANENTLY PROLONGED PR INTERVAL

In 10,000 patients with cardiac symptoms or signs, White<sup>53</sup> diagnosed A-V block in 641 cases (6.4 per cent). It was complete in 79 cases (12 per cent) and partial in 562 cases (88 per cent). In an electrocardiographic study of 4,264 patients, Logue and Hanson<sup>54</sup> found an incidence of 2.3 per cent in cases exhibiting various degrees of heart block. Another series<sup>55</sup> included an incidence of 1.5 per cent in 1,812 normal males (PR intervals above 0.20 second). The causes for auricular-ventricular conduction delays usually occur as follows: rheumatic fever, coronary disease, congenital defects, digitalis, lues, vagotonia, or fatigue following extreme tachycardiac. Asphyxia, quinidine, hyperthyroidism, uremia, various poisons and diphtheria may also produce a prolongation of the A-V interval. Rarely, bacterial endocarditis, neoplasms, miliary tuberculosis and trauma may be etiologic factors.

When rheumatic fever is the cause, the A-V delay may persist for hours to weeks but usually clears up entirely. Electrocardiograms are necessary to diagnose first degree heart block since it is extremely difficult to make the diagnosis clinically. However, suspicion may be aroused if there is a gallop rhythm or a decreased intensity of the first heart sound. Complete heart block is attended by a slow regular ventricular rate, syncopal attacks and changing quality and intensity of the first heart sound due to changing relationships of the auricular and ventricular contractions. Its main danger lies in attacks of Adams-Stokes syndrome or sudden death. Serial electrocardiography is important in following the course of A-V conduction delays. After a variable period the PR interval returns to normal. The histamine,<sup>55a</sup> vagal pressure and atropine tests are of considerable importance in evaluating the cause of the increased PR interval and are used routinely by us in cases with prolonged PR intervals or suspected rheumatic activity.

A PR interval over 0.21 second is considered abnormal. The significance of a possible vagus effect is not clear in many cases. Pardee<sup>57</sup> was very doubtful if a vagotonia ever causes more than a transient accentuation of a condition fundamentally due to disease. Most cases of high-grade persistent block are not vagal in origin because they are unaffected by atropine.<sup>58</sup> The present belief holds that an occasional person may have an increased PR interval which is normal for him but may be due to a vagotonia. On the other hand, it is not uncommon for heart block due to rheumatic fever or other acute infections to be relieved by



atropine. In fact, serious cardiac damage is frequently found at necropsy in such instances.<sup>59</sup>

**CASE 13.** A white male, aged 47, with 20 years of military service, was admitted for routine retirement examination.

*Antecedent History.* Family history was essentially negative and personal history was negative except for the present illness. Patient had one child living and well. He had had gonorrhea in 1932 and was treated over a prolonged period of time, but there were no known complications.

*Present Illness.* Patient had "inflammatory rheumatism" during childhood which lasted one month. He developed a second rheumatic fever attack seven years ago and was hospitalized for one month. Murmurs were discovered at that time but he was allowed to play in the band. With the decreased work load he had no difficulties or complaints such as dyspnea, cyanosis, edema, cough, expectorations, etc. He had no complaints at the time of admission.

*Physical examination* showed moderately severe varicosities of both lower legs, more marked on the right but without evidence of phlebitis. Heart revealed a point of maximum impulse in the fifth intercostal space just outside the midclavicular line. Heart tones were of good myocardial quality. A faint systolic and a fairly loud diastolic murmur were heard over the aortic area with downward transmission of the diastolic component. A systolic murmur at the apex was transmitted toward the axilla. An apical presystolic murmur could not be elicited following exercise or in the recumbent position. There was no cyanosis or dyspnea after the exercise test. Blood pressure was 122/62.

*Laboratory Status.* Two EKG studies performed two weeks apart in 1941 were similar. The rate was 68, inverted T<sub>s</sub>, normal sinus rhythm, left-axis deviation of minus 35 degrees, and PR interval 0.22 second. The A-V conduction delay was also found on a hospital admission in 1941 and again in 1945. It was not influenced by atropine, histamine or right and left vagal pressure. Chest x-ray revealed moderate enlargement of the transverse diameter of the heart with predominant involvement of the left ventricle. Remainder of workup was noncontributory. Final diagnosis was aortic insufficiency and stenosis and mitral insufficiency with permanent first degree A-V conduction delay due to old rheumatic fever.

## NEUROLOGIC MANIFESTATIONS AND RHEUMATIC FEVER

### PSYCHOGENIC RHEUMATISM

The term "psychogenic rheumatism" is employed when stiffness, pain, swelling or limitation of motion of the muscles or joints is caused, intensified or continued by mental processes. On the other hand it is well to remember that psychosomatic factors, such as grief and worry, may influence attacks of rheumatic fever or rheumatoid arthritis. Therefore, psychiatric examination and psychotherapy are frequently necessary for the proper management of these conditions.

The following case is of interest because the patient had an underlying history of rheumatic fever with evi-

dence of aortic insufficiency. Nevertheless, repeated clinical and laboratory studies ruled out the presence of rheumatic activity at the time of the joint complaints. A psychiatrist made a diagnosis of a moderately severe reactive depression with fixation on the joints, after organic pathology was excluded. This is an excellent example of "psychogenic rheumatism" superimposed on inactive rheumatic heart disease.

**CASE 14.** A white male, aged 29, with three and a half years of military service, was referred because of chronic joint complaints.

*Antecedent History.* He had scarlet fever, measles and whooping cough, and believed that he returned to work too soon after the attack of scarlet fever. This resulted in "dropsy" which kept him in bed for two weeks. The swelling was present over the legs, head and abdomen. He had influenza in 1919. Herniotomy was performed in 1935. Family history was essentially negative.

*Present Illness.* He had slight joint pains in the right knee for several years before induction. He believed this condition was aggravated while stationed in a cold, moist climate. Upon admission he had pain in the right knee and across the lower back. He stated that there was swelling and redness of the right knee during exacerbations but his other joints were uninvolved. For the past 15 months he also had pain in the right chest. This was not associated with dyspnea. He had a cough with slight expectoration especially in the mornings, which was somewhat thick but not foul or bloody.

*Physical Examination.* Blood pressure was 120/72. There were no enlargements, thrills or friction rubs. There was a diastolic murmur over the second aortic area which could be elicited only with the recommended method.<sup>34</sup> The joints were entirely negative. Reflexes were hyperactive but equal.

*Laboratory status* revealed negative bronchograms and negative x-rays of right knee, heart and lungs. Sedimentation rates, blood counts and urinalysis were repeatedly normal.

*Clinical Course.* Psychiatric examinations revealed the presence of a moderately severe reactive depression in a highly emotional male with an inferior mentality. In addition, the diagnosis of mild aortic insufficiency due to old inactive rheumatic fever was made.

### CHOREA AND PSYCHONEUROSES

Chorea occurs as an initial manifestation of rheumatic fever almost exclusively before puberty and practically never after 21 years of age.<sup>60</sup> It is associated with a milder form of rheumatic fever and the incidence of carditis is very low, unless it follows rheumatic polyarthritis or carditis. Hedley<sup>61</sup> found that 20 per cent of the children with rheumatic heart disease have histories of chorea. If there is unusually high fever, delirium may rarely be followed by coma. Delirium may progress to a transitory or fixed acute psychosis. In this connection it is well to remember that the large dosage of salicylates may in itself induce delirium.



It is often difficult to distinguish between true choreiform movements and habit spasm. The former may also be seen in such nonrheumatic conditions as poliomyelitis, birth injuries, encephalitis, tics and psychogenic disturbances.<sup>62</sup> The confusion is heightened by the fact that patients with rheumatic fever reveal a family history with a particularly high incidence of nervousness. These patients present a personality pattern that is repressed, passive and submissive with dominant extratensive tendencies and little creative inner life. Definite signs of anxiety exist just beneath the surface. They are subject to temper tantrums, nightmares, worrying and tics. In spite of many attacks of rheumatic fever including cardiac involvement, many of the patients are likely to recover but may later develop rheumatoid arthritis. In an extensive study Neustater<sup>63</sup> attempted to determine the incidence of functional disorders before and after rheumatism. Nervousness began before the age of two in 42 per cent of the cases. Joint pains were explained on the bases of prolonged fatigue and emotional strain which in turn may lower the resistance to rheumatic infections.

The following case illustrates the difficulties encountered in making the correct diagnosis in a patient with a past history of chorea. The atypical joint pains and choreiform movements of the head strongly suggested rheumatic involvement. However, the family history of marked nervousness, age, absence of cardiac involvement, negative laboratory tests and the occurrence of other psychoneurotic manifestations ruled out the presence of rheumatic fever. A re-evaluation of his original attack of "St. Vitus dance" made a diagnosis of juvenile psychoneurosis seem more likely.

**CASE 15.** A white male, aged 30, with one month of military service, entered with a multiplicity of unrelated complaints.

*Antecedent history* was significant.

**Family History:** Father was a retired farmer, 62 years of age and well. Mother was 58 years old, of "a very nervous type" and had gallstones. One brother was killed in an accident. Another brother suffered from ulcers of the stomach. Two sisters were living and well and another sister was born dead. He had no serious illness during childhood. At the age of 12 he developed "Saint Vitus dance with blinking of the eyes, twitching of face, and involuntary motions of the head." He was treated with drops of arsenic solution for three years(!). He managed to complete one year of college.

**Operations:** Tonsillectomy and adenoidectomy were performed at the age of 29.

**Injuries:** (1) In 1930 he bumped the back of his neck against the inside door of a box car. There was no fracture but it caused him pain ever since. (2) In 1938 he missed his step in the dark and fractured the left fifth metatarsal bone with tearing of ligaments and the foot remained painful ever since.

**Present Illness.** Patient was admitted in order to determine his physical fitness. He stated that he tried to do duty, but was unsuccessful because of (1) painful left foot with inability to march over rough terrain, (2) pain in occipital and lower cervical region since his first accident, (3) severe nervousness since age of 12, (4) severe headaches, and (5) palpitation of the heart.

**Physical examination** revealed marked involuntary to-and-fro movements of the head. Blood pressure was 134/80, pulse 84, and there was no evidence of cardiac disease. He had several external hemorrhoids. There was tenderness over the seventh cervical vertebra. The left fifth metatarsal bone was somewhat prominent and tender. The remainder of the examination was negative.

**Laboratory Status.** Blood serology, blood counts, urinalysis, x-rays of chest, cervical spine and left foot were entirely negative. Special examinations: Dental consultation showed an ill fitting denture which was corrected. Orthopedic consultation: Findings did not justify an orthopedic disposition but it was doubted whether the soldier would be able to continue in the army.

**Course in the Hospital.** There was no change in the physical or mental condition during his hospital stay. He continued to have choreiform movements of the head, palpitation, tachycardia, hyperhidrosis of hands, and tenderness over the fifth metatarsal bone and over the seventh cervical vertebra. His nervous condition was marked and he complained of persistent occipital headaches. The final diagnosis was severe psychoneurosis of the anxiety type.

#### EPILEPSY AND RHEUMATIC HEART DISEASE

When a rheumatic valvular lesion is discovered (as in the following case) and nervous manifestations co-exist, a differentiation must be made between a rheumatic manifestation and epilepsy since either may involve the motor cortex. In chorea, typical lesions with Aschoff bodies are never present. Perivascular collections of round cells with endothelial proliferation and thrombosis occurring in the corpus striatum, cortex and meninges are present in the form of a meningo-encephalitis. The possible causes for epilepsy are legion. However, the occurrence of neurologic manifestations after 21 years of age tends to rule out chorea almost completely.<sup>60</sup> Laboratory studies excluded rheumatic activity in the following case despite the presence of an old mitral lesion.

**CASE 16.** A Puerto Rican male, aged 28, with eight months of military service, was admitted with complaints referable to the respiratory system.

**Antecedent History.** Father died of heart trouble at 54 years. Mother died at 51 years of unknown cause. Two brothers committed suicide, one of whom was a chronic alcoholic. One sister was living and well. Patient's habits were good. Measles and mumps occurred during childhood. He broke a leg at the age of nine.

**Present Illness.** For the past two months the patient noticed some increased shortness of breath on exercise and cough with slight mucopurulent expectoration but no blood and there was no ankle edema. No urinary complaints were elicited. Rheumatic fever history was entirely

negative and he was never told of any cardiac involvement. Patient had epileptic seizures for six or seven years which began with tingling on the left side of the body and twitching of left shoulder followed by unconsciousness. He bit his tongue occasionally. His last attack occurred two years ago.

*Physical Examination.* Blood pressure was 120/80. Heart revealed no enlargements and regular sinus rhythm was present. Heart tones were of good myocardial quality without thrill or friction rubs. There was a systolic blow over the precordium, heard loudest at the apex, which did not disappear after exercise and was transmitted toward the axilla.  $P_2$  was slightly accentuated and greater than  $A_2$ . Reflexes were hyperactive, especially on the left side. The left knee jerk showed clonus. Examination of the chest wall revealed no masses, tenderness, or redness.

*Laboratory Status.* The EKG was normal. Fluoroscopy and x-rays of the heart were normal. An area of destruction, approximately 6 cm. in length involving the posterior portion of the left fifth rib, was noted. There was no break in the cortex and it appeared to have the characteristics of a benign tumor of the giant cell type. Blood calcium, phosphorus and phosphatase were normal. Cholesterol was 214 mg. per cent. Complete blood studies were negative for blood dyscrasia. The patient was transferred for further treatment of the bone lesion. The final diagnoses were (1) mitral insufficiency due to old rheumatic fever, (2) grand mal epilepsy and, (3) giant cell tumor of the left fifth rib.

### PALINDROMIC RHEUMATISM

Palindromic ("recurring") rheumatism was first described by Hench and Rosenberg.<sup>64</sup> Briefly, it consists of numerous afebrile attacks of inflammation in and around the joints which appear suddenly and disappear in several hours to a few days. There is little or no constitutional reaction. Even after years, no pathologic or roentgenographic changes are noted despite the possible occurrence of an acute inflammatory exudate in and about the articular surfaces. There is complete remission between these attacks which may number in the hundreds. Any joint may be involved but the hands are most frequently affected. The knees, feet, wrists and shoulders are often involved. The sedimentation rate is slightly elevated in about 60 per cent of the cases and there is usually a relative lymphocytosis. It is most frequently confused with rheumatoid arthritis and rheumatic fever. Following is a typical case in point. The admission diagnosis was rheumatic fever but a careful history, the clinical course and completely negative laboratory studies, established a diagnosis of palindromic rheumatism.

**CASE 17.** A white male, aged 32, with 13 months of military service, was admitted with a history of frequent joint pains.

*Antecedent History.* Patient was a furniture salesman and collector before induction 13 months ago. Habits were good. Family history was negative except for father

who committed suicide at 40 years because of ill health. Mother died at 30 years from an unknown cause.

Whooping cough and mumps occurred during childhood. An attack of measles was exceptionally severe at the age of six resulting in incapacitation for five months and "settled in the bowels and kidneys." Surgical operations and venereal disease were denied.

*Present Illness.* For the past seven years the patient was troubled with painful joints. Occasionally the joint pains would be followed by a painful eruption in the neighborhood of the joint which would last from a few hours to four or five days. The joints would swell but involved only one joint at a time. In October 1944 he was hospitalized because of pain, redness and swelling of the right knee. The left knee and left index finger were later involved. On 4 December 1944 he was again hospitalized because of pain and puffiness about the second joint of the left ring finger. Repeated x-rays were entirely negative. The white count, sedimentation rates and blood uric acid were normal. Calcium gluconate (10 cc. intravenously daily) failed to produce any improvement since he suffered another attack one week later while receiving this treatment. He was not free from joint involvement for more than one month in the last six years. On 16 March 1945 patient was admitted to this hospital because of pain and redness of the right knee.

*Physical examination* revealed a fairly well demarcated erythematous slightly raised areas over both heels and dorsum of right wrist. They were tender and about the size of silver dollars. There was slight pain and immobilization without definite swelling or heat of the right wrist. The other joints were negative. Heart was entirely negative. Blood pressure was 104/56. There were no tophi, bursitis or tenosynovitis.

*Laboratory Status.* EKG was negative except for sinus tachycardia. At a previous examination, there was also a negative EKG reported. X-rays of the chest, heart, pelvis, sacro-iliac and hip joints, small joints of the hand and right knee were entirely negative. On the medial surface of the upper portion of the shaft of the right fibula, there was a spinelike projection of bone typical of osteoma. Sedimentation rates never rose above 20 mm. per hour. Urinalyses were negative. White blood count was 6,500 with a differential of 66 per cent neutrophils and 33 per cent lymphocytes, and hemoglobin was 90 per cent. Blood culture was sterile. Blood uric acid was 3.6 mg. per cent. The Kahn test was negative. Heterophile antibody titer was negative. Platelet count was 310,000 per cu.mm., bleeding time 2 minutes and clotting time 5 minutes.

*Special Examinations.* GU consultation revealed no evidence of focal infection in the prostate or seminal vesicles. Dental examination revealed no significant findings. Undulant fever agglutination and tuberculin tests were negative. EKG revealed no deviations from the normal after prostigmin (1 cc. hypodermically).

*Clinical Course.* During his hospital stay, he suffered two exacerbations which lasted from one to four days. The erythematous areas abated without going through color changes but were accompanied by considerable aching and throbbing for a period of about four days. They cleared spontaneously without any specific medication. There was no temperature elevation during the entire stay. The final diagnosis was palindromic rheumatism and erythema multiforme.

## SUMMARY AND CONCLUSIONS

1. Although acute rheumatic fever is more prevalent in northern climates there is a much greater percentage of atypical forms in southern areas which present difficulties in diagnosis.

2. Case histories and discussions of several unusual manifestations of acute rheumatic fever are presented under one title to emphasize its protean character. Early recognition of atypical forms may minimize permanent damage when treated with large doses of salicylates.

3. Rheumatic peritonitis may give rise to a mistaken diagnosis of acute appendicitis. Although it is a fairly commonly recognized mild manifestation in children, it occasions needless surgery in adults because of its rarity.

4. Rheumatic pneumonia may be overlooked at the height of infection because of its transitory nature and paucity of specific symptoms and signs. The diagnosis usually rests on finding signs of migratory pulmonary exudates or typical serial x-ray changes.

5. The occurrence of glomerulonephritis during an attack of acute rheumatic fever in two cases contributes further evidence to the possible basic rôle of renal vascular injury in the hypersensitive state.

6. Atypical arthritic involvement frequently results in mistaken diagnosis. A full-blown rheumatic fever attack frequently develops in cases beginning with a history of "sprained ankle," atypical monarticular involvement of small joints such as the astragalus, or atypical large joints such as the sacro-iliac.

7. A case of Reiter's disease superimposed on old rheumatic heart disease is presented. The development of the triad of nonspecific urethritis, conjunctivitis and arthritis establishes the correct diagnosis. The cause is unknown and there is no specific therapy at present. There is no known relationship with rheumatic fever or gonorrhea.

8. The proper method of examination for detection of minimal involvement of the aortic valve is reiterated. Earlier diagnosis can be made, based on the murmur alone and before the development of other corroborative signs.

9. Confusing similarities between rheumatic fever and rheumatoid arthritis and epiphysitis are discussed. Early management of these conditions prevents crippling deformities of the heart or joints.

10. The possibility of an atypical source of infection in the causation of rheumatic fever is discussed. An example of rheumatic exacerbation, probably caused by cellulitis of an extremity with lymphoid invasion, is presented.

11. The importance of differential diagnosis of a permanently prolonged PR interval is included.

12. A discussion of the psychosomatic influences of rheumatic fever is presented. Psychogenic rheumatism, epilepsy, choreiform movements and the psychoneuroses are differentiated from rheumatic fever activity.

13. A case of palindromic rheumatism with erythema multiforme is presented. The importance of a careful history and the clinical course is emphasized in its differentiation from rheumatic fever and rheumatoid arthritis.

14. Salicylates in high dosage should be continued for a short interval following subsidence of acute rheumatic fever to avoid exacerbations and prolonged convalescent periods.

## BIBLIOGRAPHY

1. Comroe, B. I.: *Arthritis and Allied Conditions*, ed. 3, Philadelphia, Lea & Febiger, 1944, p. 777.
2. Paul, J. R., and G. L. Dixon: Climate and rheumatic heart disease; survey among American Indian school children in northern and southern localities, *J. A. M. A.*, 108:2096, 1937.
3. Coburn, A. F.: Salicylate therapy in rheumatic fever: rational technic, *Bull. Johns Hopkins Hosp.*, 73:435 (Dec.) 1943.
4. Manchester, R. C.: Rheumatic fever in naval enlisted personnel, *J. A. M. A.*, 131:209 (May 18) 1946.
- 4a. Andral: *Précis d'anatomie pathologique*. (—) *Compendio d'anatomia patologica*. Nuova versione italiana del Livorno, Gamba, 1839. (Ermenegildo canigiani sull'ultima edizione francese IV, 5-590, p. 31.)
5. Geptill, P.: Differential diagnosis of abdominal manifestations of acute rheumatic fever from appendicitis, *Ann. Surg.*, 99:650, 1934.
6. Wolffe, J. B., and C. J. Brim: Abdominal syndrome of rheumatic disease in childhood, *Am. J. Dis. Child.*, 52:296, 1936.
7. Wood, F. C., and E. L. Eliason: Rheumatic peritonitis, *Am. J. Med. Sci.*, 181:482, 1931.
8. Still, G. F.: *Common Disorders and Diseases of Childhood*, ed. 2, London, Henry Frowde, 1912.
9. Pearson, S. V.: Abdominal pain in acute rheumatism, *Brit. Med. J.*, 1:1120, 1904.
10. Poynton, F. J.: *Osler's Modern Medicine* (McCrea), ed. 3, Philadelphia, Lea & Febiger, 1925, ii, p. 187.
11. Graham, R. S., and J. R. Paul: Studies in rheumatic fever; I. A brief review of clinical and gross pathological findings in eighteen fatal cases, *Bull. Ayre Clin. Lab.*, 10:44, 1926.
12. Baggage, D. E., C. W. McLaughlin, Jr., and I. L. Fruin: Strain of right rectus muscle simulating acute appendicitis, *War Med.*, 5:280, 1944.
13. Reitman, N.: Abdominal manifestations of rheumatic fever: description of a right rectus syndrome, *Ann. Int. Med.*, 22:671, 1945.
14. von Glahn, W. C., and A. M. Pappenheimer: Specific lesions of peripheral blood vessels in rheumatism, *Am. J. Path.*, 2:235, 1926.
15. Naish, A. E.: Rheumatic lung, *Lancet*, 2:10, 1928.
16. Gouilly, A. M., and J. Eiman: Pathology of rheumatic pneumonia, *Am. J. Med. Sci.*, 183:359, 1932.

17. Gray, J. W., E. Fendrick, and C. H. Gowen: Rheumatic fever and rheumatoid arthritis, *Texas State J. Med.*, 28:203, 1932.
18. Bell, E. T.: Glomerular lesions associated with endocarditis, *Am. Jour. Path.*, 8:639, 1932.
19. Rolly: *Die Akute Gelenkrheumatismus*, Berlin, Springer, 1920, p. 65.
20. Libman, E.: Characterization of various forms of endocarditis, *J. A. M. A.*, 80:813, 1923.
21. Goldring, W., and J. Wyckoff: Studies of kidney in acute infection; observations with urine sediment count (Addis) in acute rheumatic infection, *Jour. Clin. Invest.*, 8:569, 1930.
22. Baehr, G., and —. Schifrin: The rarity of glomerulonephritis in rheumatic fever and its significance, *Libman Anniversary Volumes*, New York, 1:125, 1932.
23. Fishberg, A. M.: *Hypertension and Nephritis*, ed. 4, Philadelphia, Lea & Febiger, 1944, p. 429.
24. Hutton, R. L., and C. R. Brown: Renal lesions in rheumatic fever, *Ann. Int. Med.*, 20:85, 1944.
25. Klinge, F.: *Der Rheumatismus: pathologisch-anatomische und experimentell-pathologische tatsachen und ihre Auswertung für das ärztliche Rheumaproblem*, *Ergeb. d. Allg. Path. u. Path. Anat.*, 27:1, 1933.
26. Rossle, R.: Zum Formenkreis der rheumatischen Gewebsveränderungen, mit besonderer Berücksichtigung der rheumatischen Gefässentzündung, *Virch. Arch. f. Path. Anat.*, 288:780, 1933.
27. Salversen, H. A.: Rheumatic fever and nephritis. Clinical contributions to question of rheumatic nephritis, *Acta Med. Scandinav.*, 96:304, 1938.
28. Uzan, M.: Contribution a l'etude clinique et therapeutique des determinations renales du rhumatisme articulaire aigu, Paris, Jouve et Cie, 1922.
29. Boyd, Wm.: *Pathology of Internal Diseases*, ed. 4, Philadelphia, Lea & Febiger, 1944, p. 393.
30. Gersh, I., and N. E. Reich: Arthritis, urethritis and conjunctivitis (Reiter's disease), *Urol. & Cut. Rev.*, 49:472, 1945.
31. Reiter, H.: Ueber ein bisher unerkannte Spirochaetinfektion (Spirochaetosis Arthritica), *Deutsch. Med. Wchnschr.*, 42:1535, 1916.
32. Bauer, W., and E. P. Engleman: A syndrome of unknown etiology characterized by urethritis, conjunctivitis and arthritis (so-called Reiter's Disease), *Tr. Assn. Am. Phys.*, 57:307, 1942.
33. Colby, F. H.: Renal complications of Reiter's disease, *J. Urol.*, 52:415, 1944.
34. Reich, N. E.: The early recognition of minimal aortic insufficiency, *Am. Pract.*, 1:475, 1947.
35. White, P. D.: *Heart Disease*, ed. 2, New York, Macmillan, 1938, p. 445.
36. Reich, N. E.: Calcific aortic valve stenosis: A clinico-pathologic correlation of 22 cases, *Ann. Int. Med.*, 22:236, 1945.
37. Boyer, N. H., R. W. Eckstein, and C. J. Wiggers: Characteristics of normal heart sounds recorded by direct methods, *Am. Heart J.*, 19:257, 1940.
38. Bartlett, W. M., and J. B. Carter: Combined electrocardiography, stethography and cardioscopy in the early diagnosis of heart disease, *Ann. Int. Med.*, 19:271, 1943.
39. Reich, N. E.: Dissecting aneurysms of the aorta: A clinico-pathologic correlation of 19 cases, *Clinics*, 3:346, 1944.
40. Comroe, B. I.: *Op. cit.*, p. 798.
41. Bayles, T. B.: Rheumatoid arthritis and rheumatic heart disease in autopsied cases, *Am. J. Med. Sci.*, 205:42, 1943; Rheumatic heart disease in autopsied cases of rheumatoid arthritis (abstract), *Ann. Int. Med.*, 19:113, 1943.
42. Baggenstoss, A. H., and E. F. Rosenberg: Visceral lesions associated with chronic infectious (rheumatoid) arthritis, *Arch. Path.*, 35:503, 1943.
43. —: Cardiac lesions associated with chronic infectious arthritis, *Arch. Int. Med.*, 67:241, 1941.
44. —: Cardiac lesion in chronic infectious (rheumatoid) arthritis, *Proc. Staff Meet. Mayo Clin.*, 16:232, 1941.
45. Conrad, C. K.: Gonococcus filtrate (Corbus-Ferry) as skin sensitization test for gonorrhea, *New York State J. Med.*, 36:1767, 1936.
46. Bennett, G. A.: Comparison of pathology of rheumatic fever and rheumatoid arthritis, *Ann. Int. Med.*, 19:111, 1943.
47. Hench, P. S.: Rheumatism and arthritis, review of American and English literature for 1940 (eighth rheumatic review), *Ann. Int. Med.*, 15:1002, 1941.
48. Master, A. M., H. L. Jaffee, and S. Dack: The occurrence of rheumatic fever in a patient with rheumatoid arthritis, *J. Mt. Sinai Hosp.*, 4:141, 1937.
49. Comroe, B. I.: *Op. cit.*, p. 769.
- 49a. Vontz, O.: *Deutsch. med. Wchnschr.*, 63:1558, 1937.
50. Menzer, A. A. L.: Das Antistreptokokkenserum und seine Anwendung beim Menschen, *München Med. Wchnschr.*, 50:1057, 1903.
51. Cecil, R. L.: *Op. cit.*, p. 503.
52. Dunbar, F.: *Psychosomatic Diagnosis*, New York, Hoeber, 1943, p. 373.
53. White, P. D.: *Op. cit.*, p. 673.
54. Logue, R. B., and J. F. Hanson: Heart block. A study of 100 cases with prolonged P-R interval, *Am. J. Med. Sci.*, 207:765 (June) 1944.
55. Ferguson, D., and J. T. O'Connell: Cardiovascular observations, including series of electrocardiograms of 1,812 men without heart symptoms, *U. S. Naval Med. Bull.*, 24:860, 1926.
- 55a. Gubner, R., M. Szucs, and H. E. Ungerleider: Provocative prolongation of the P-R interval in rheumatic fever, *Am. J. Med. Sci.*, 209:469, 1945.
56. Katz, L. N.: *Electrocardiography*, Philadelphia, Lea & Febiger, 1941.
57. Pardee, H. E.: *Clinical Aspects of Electrocardiography*, New York, Hoeber, 1941.
58. Lewis, Sir Thomas: *Diseases of the Heart*, ed. 2, New York, Macmillan, 1937, p. 94.
59. Carter, E., and F. R. Dieudade: Recurrent complete heart block with normal conduction between attacks, *Bull. Johns Hopkins Hosp.*, 34:401, 1923.
60. Cecil, R.: *Op. cit.*, p. 444.
61. Hedley, O. F.: *Rheumatic Heart Disease in Philadelphia Hospitals*, Reprint No. 2195, U. S. P. H. S., Washington, D. C., 1941.
62. Dunbar, F.: *Op. cit.*, p. 433.
63. Neustater, W. L.: Nature and relationship of functional nervous disorders to rheumatism in childhood, *Guy's Hosp. Rep.*, 87:8, 1937.
64. Hench, P. S., and E. F. Rosenberg: Palindromic rheumatism, *Arch. Int. Med.*, 73:293, 1944.

# EDITORIAL . . .

## First Anniversary

With this issue, the first volume and the first year of the AMERICAN PRACTITIONER are completed. It is believed that it has had a reasonable degree of success in meeting its announced objective, "to provide sound and helpful articles which present the best current thought and practice in the various fields of general medicine," particularly, "as reflected in the current teaching of the . . . faculties and staffs of medical schools and of centers . . . of medical education." It is hoped that the subscribers and readers agree with this belief.

Some indication of the fulfillment of these objectives is shown by the fact that a large proportion of the papers which have been selected for publication have been based on material presented at well-established professional meetings, in postgraduate and graduate courses given at our leading medical schools, at clinics and at medical centers, or, by the faculties and staffs of such institutions. Evidence of the approval of the material which has been published is shown by the constantly increasing number of subscribers, and the numerous favorable and critical comments which have been received from subscribers and readers.

The editors and publishers are conscious of their opportunity and their obligation to make the AMERICAN PRACTITIONER even more interesting, instructive and valuable to its subscribers and readers.

In particular, they are anxious that it be of greater service in meeting the practical needs of the physician in general medicine. For this reason they are looking forward to greater reader participation and the presentation of their views and opinions. They are also

concerned with giving better service to the physician in the way of providing authoritative information on recent scientific advances or developments. In regard to the latter it should be pointed out that the expression "Shortening the lag between experiment and practice" does not necessarily mean that every new development reported at meetings or in the scientific or lay press should be transmitted at once to readers and subscribers as ready for immediate practical application. The "shortening" is relative and the time required to evaluate new concepts and procedures and determine their place in practice is variable. For some things it may require weeks or months, for others, years. Nevertheless, there should be less delay than often does occur and in the necessary waiting period it is important that the practicing physician be equipped with authoritative information concerning matters of medical interest appearing in the current news and about which his patients inquire.

In order to provide this additional service and make the AMERICAN PRACTITIONER an even better medium of information and continuing education it will be increased to 80 pages. A department dealing with current items of medical interest is planned. While the latter cannot be expected to include all such items which appear in the current news, an attempt will be made to present each month some of the more significant.

The editor wishes to take this occasion to thank the subscribers and readers for their interest and the many helpful criticisms as well as the expressions of approval.

# AMERICAN PRACTITIONER

Volume I

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*Phlebothrombosis and its complication of embolism is described, with a discussion of treatment. In consideration of the use of anticoagulants the author points to the dangers in their use unless adequate laboratory control is available.*

## Phlebothrombosis—Operative and Nonoperative Treatment\*

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Thrombophlebitis of the lower extremities has long been known as a complication of the puerperium as its name of "milk-leg" indicates. The clinical picture of a painful, tender, swollen, rather pale and sweaty leg, with a palpable, tender femoral vein and fever is very characteristic and familiar. The thrombus which is present is adherent to the vein wall, causing irritation and reflex vasospasm. The tendency toward the formation of a massive pulmonary embolus is probably not very great in these cases.

Less well known is the state which so frequently precedes the full-blown picture. A thrombus forms in the veins of the leg or foot and propagates itself without becoming adherent to the wall of the vein and without causing the reflex vasospastic phenomena. The thrombus is long, jelly-like and friable and is readily detached to form a pulmonary embolus. The clinical findings in such a "bland thrombosis" or phlebothrombosis may be quite meager. Tenderness may be present along the plantar veins, and is more commonly present in the calf. Homan's sign (dorsiflexion of the foot while the knee is in extension causing pain in the calf when thromboses are present in the calf veins) is often positive. Slight to moderate edema occurs frequently. The patient may not complain of the leg at all, and the mild pain and the other signs that are present may not be discovered unless the patient is questioned routinely or until attention is directed toward the legs after an episode of pulmonary embolism. Phlebothrombosis progresses toward thrombophlebitis, and between the two clinical syndromes one may see intermediate stages.

Phlebothrombosis is less well recognized as a complication in medical cases, but it is a frequent compli-

cation in congestive heart failure, Buerger's disease and some other peripheral vascular diseases, polycythemia and some acute infections.

Venous thrombosis is a common complication in surgery, since the coagulability of the blood increases after trauma and after operations, and since stagnation of venous flow in the legs occurs constantly in very ill patients confined to bed. Postoperative surgical deaths due to shock, infection and malnutrition have shown a steady decrease. Hence the number of deaths due to pulmonary embolism has shown a relative increase. Furthermore, since control of shock, infection and malnutrition has extended the limits of operability in older age groups, the actual number of embolic deaths has probably increased due to the high incidence of embolic phenomena found in the elderly.

### DIAGNOSIS

For the general practitioner it is important to know that a considerable number of instances of thrombosis in the deep veins of the legs occur without obvious cause in individuals who are apparently well and who are engaged in their normal pursuits. A history of mild pain in the leg, with slight swelling should alert the physician to the possibility of thrombosis.

The location and the actual extent of venous thrombosis is often a problem. When a clear-cut femoral thrombophlebitis is present on one side, careful search must be made on the opposite side for evidences of phlebothrombosis. This is of especial importance since the "silent" side is more likely to be the source of emboli. Bilateral involvement is about as common as unilateral involvement.

When a minor pulmonary embolism occurs the lower extremities must be carefully examined for evidence of phlebothrombosis. Better still, routine examination of the legs in all patients confined to bed should be instituted.

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## PROPHYLAXIS

Prevention of thrombosis is important. Leg exercises, elastic bandaging and the avoidance of unnecessary confinement to bed have been advocated. In certain conditions known to be frequently complicated by thrombosis and embolism such as cardiac decompensation, extensive operations for malignant abdominal disease in the elderly, and fractures about the hip, more definite prophylactic measures should be considered. These are the use of anticoagulants and prophylactic femoral ligation. Anticoagulants are to be preferred in the nonoperative cases and ligation in the cases which will require one or more operations. However, in special situations such as operations primarily for vascular disease (mesenteric thrombosis, arterial embolism, etc.) anticoagulant therapy is indicated. No single rule can be laid down.

## TREATMENT

**Ligation Proximal to the Thrombus.** Ligation of the involved vein proximal to the thrombus effectively prevents the thrombus from causing embolism. The level for operation is determined by the extent of the thrombosis.<sup>1</sup> When the process appears to extend no further than the knee, ligation of the femoral vein just below the profunda tributary is preferred. When the process extends above this level, ligation of the common femoral, external, or common iliac veins must be considered. Ligation of the vena cava may be considered when a bilateral process would require ligation of both common iliac veins, or when the process involves the pelvic veins. Considerable numbers of caval ligations have been reported recently.<sup>2-4</sup> Very little edema and disability seem to follow the operation.

Bilateral involvement of the lower extremities occurs very frequently and bilateral ligation should be considered in certain patients even when one side seems asymptomatic. An embolus may originate from the silent side that shows minimal clinical signs.

**Anticoagulants (Heparin and Dicoumarol).** It has been shown that the thrombotic process can be effectively stopped by administration of anticoagulants in proper dosage. The drug of choice for this purpose is dicoumarol, which is given by mouth. Since it takes about two or three days for the drug to become effective, heparin is used during this latent period. When an immediate effect is desired, 5 cc. (50 mg.) of heparin is given intravenously, followed by 5 cc. intramuscularly every four hours. Coagulation times are determined about three or four hours after each dose by a modified Lee-White method (a time of

15 to 30 minutes is desirable). Heparin is continued until a satisfactory prothrombin level is produced by dicoumarol. Heparin in Pitkin's menstruum, for prolonged action, has been used<sup>5</sup> and it seems likely that a preparation can be evolved which will require only single daily doses. Dicoumarol, 300 mg., is given on the first day, 200 mg. on the second day, and 100 mg. daily thereafter as guided by the prothrombin level. The optimum level is from 20 to 30 per cent of normal, although anticoagulant effect is present at higher levels. The danger of hemorrhage, the chief hazard in the use of the drug, is usually not great until the level is below 10 per cent of normal.<sup>6</sup> When the daily prothrombin level is too low, the dose for that day is omitted; if the level is too high, the dose is increased. The dicoumarol should be given until the patient becomes ambulatory and then the dose is tapered off. The drug may be given for many weeks or months if the prothrombin level is properly controlled. In these instances, less frequent determinations may be done.

When hemorrhage appears to threaten because of unusually low prothrombin levels, the level can be raised by the intravenous administration of 64 mg. synthetic vitamin K (hykinone). When bleeding actually occurs, a transfusion of 500 cc. of fresh citrated blood should be given in addition, and repeated daily or more frequently if bleeding continues.

Heparin alone has been used as the anticoagulant in Scandinavian clinics<sup>7</sup> in amounts of 350 to 450 mg. daily, divided into four intravenous injections given at 8 A.M., 12 noon, 4 P.M., and 8 P.M. or 10 P.M., in amounts of 125, 100, 100, and 125 mg. On the third day the dose is lowered to 300 to 350 mg. This author<sup>7</sup> remarks that heparin has been used this way without determining coagulation times and that the risk involved seems small. This method seems promising and further reports will be awaited with interest. If dicoumarol was previously started, heparin is stopped when the prothrombin level becomes satisfactory.

**Considerations Governing the Choice of Treatment.** Anticoagulant therapy would appear to be indicated as a prophylactic measure in certain patients, such as those with heart disease, and as the treatment of choice in embolic episodes when the source of the emboli is unknown or in doubt. It would also be useful in those instances in which the risk of operation appears unduly great. It can be used when embolic episodes occur after ligation.

While anticoagulant therapy could be used in definitely localized phlebothrombosis and thrombophlebitis, it would appear that ligation above the thrombus

offers the patient greater protection against the danger of an embolus. Ligation seems clearly indicated in those patients who have a minor embolism originating from the leg veins.

Both methods have their disadvantages. Anticoagulant therapy requires constant supervision and accurate laboratory work. There is danger of serious hemorrhage in postoperative patients. It does not prevent already formed thrombi from breaking off, so that embolic episodes may occur during administration or after stopping the drug. Dicoumarol should not be used in the presence of advanced renal disease, when there is impaired liver function or a known tendency toward bleeding.

Ligation above the thrombus may entail a formidable surgical procedure. It does not prevent thrombi from forming above the ligature, or elsewhere in the body, as is the case with anticoagulants. Ligations can be safely performed under certain conditions which make anticoagulant therapy very dangerous.

The treatment chosen in any particular case should be that offering the maximum protection from fatal embolism with the minimum risk of a serious complication.

The local treatment of the legs involved in a thrombotic or phlebitic process may require lumbar symp-

thetic procaine injections, pressure dressings and other measures which will be considered in another publication.

## BIBLIOGRAPHY

1. Allen, Arthur W.: Interruption of the deep veins of the lower extremities in the prevention and treatment of thrombosis and embolism, *Surg. Gynec. & Obstet.*, 84:519-527 (April) 1947.
2. Ochsner, Alton: Venous thrombosis, *J. A. M. A.*, 132: 827-834 (Dec.) 1946.
3. Thebaut, Ben R., and Charles S. Ward: Ligation of the inferior vena cava in thromboembolism, report of 36 cases, *Surg. Gynec. & Obstet.*, 84:385-401 (April) 1947.
4. Veal, J. Ross, Hugh Hudson Hussey, and Earl Barnes: Ligation of the inferior vena cava in thrombosis of the deep veins of the lower extremities, *Surg. Gynec. & Obstet.*, 84:605-610 (April) 1947.
5. Evans, James A., and Raymond J. Bolter: The subcutaneous use of heparin in anticoagulation therapy, *J. A. M. A.*, 131:879-881 (July) 1946.
6. Barker, Nelson W., Horace E. Cromer, Margaret Hurn, and John M. Waugh: The use of dicoumarol in the prevention of postoperative thrombosis and embolism with special reference to dosage and safe administration, *Surgery*, 17:207-217, 1945.
7. Jorpes, J. Erik: Anticoagulant therapy in thrombosis, *Surg. Gynec. & Obstet.*, 84:677-681 (April) 1947.

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## The Doctors' Health

The life expectancy of the average young doctor entering practice at the age of 25 is 43.5 years according to a recently published survey by Dr. Louis I. Dublin of the Metropolitan Life Insurance Co. Such a life expectancy is very nearly the same as that for white men of the same age in any business or profession.

However, the doctor takes advantage of his special training and skills to avoid some of the ills that trouble the general population. For instance, the tuberculosis death rate among male doctors is less than half that for other men; cancer, four-fifths; syphilis, one-third; appendicitis and hernia, three-fourths; automobile accidents, nine-tenths; other accidents, three-fourths.

On the other hand, physicians experience a higher mortality from cardiovascular diseases. Diseases of the coronary arteries account for the death of 1.8 times as many physicians as other white males. The higher mortality from leukemia (1.75) is not easily explained although it has recently been suggested that this may be due to the greater exposure of some doctors to x-rays.



## A Synopsis of Present Concepts in Endocrinology\*

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In the following discussion I have attempted to summarize the present understanding of the abnormal function of certain endocrine glands and the treatment indicated in these cases.

### THYROID

**Simple Goiter.** The importance of iodine in the prevention of simple goiter is still recognized. Unfortunately, there is no systematic protection of the population in most goiter belts, inasmuch as the use of iodized salt is entirely optional and is not even urged unless the doctor assumes this responsibility. Iodine, supplied in this small quantity, is an essential dietary element rather than a drug. There is no basis for the old belief that thyrotoxicosis might be precipitated by the use of iodized salt.

**Hypothyroidism.** The familiar clinical features of myxedema need no recounting. It is a striking fact, however, that the diagnosis is frequently missed because it is simply not thought of. Once the disease is suspected the low BMR and high plasma cholesterol afford convincing laboratory confirmation. It should be emphasized that marked obesity is not a feature of myxedema. The weight gain is due largely to fluid retention.

In the therapy of the disease it is best to begin with  $\frac{1}{4}$  gr. doses of desiccated thyroid and increase slowly to 2 or 3 gr. over a period of several months. High initial doses may produce anginoid pain.

Thyroid therapy is often useful in a number of other conditions accompanied by a low BMR, but which cannot be called true myxedema. It is true that many normal persons have a metabolism as low as -20. If, however, a severe hypometabolism is accompanied by disorders such as menstrual abnormalities, lethargy, obesity, acne, furunculosis, sterility, etc., thyroid therapy should be tried. Patients with simple obesity and a normal BMR should usually not be treated with thyroid. Any tendency toward combustion of fat induced by safe doses is offset by increased appetite. Treatment should consist of a diet of 800

to 1,000 calories with or without anti-appetite drugs, and a search should be made for psychologic factors which might induce an abnormal craving for food.

**Hyperthyroidism.** There are no new practical shortcuts useful in the diagnosis of thyrotoxicosis. It should be emphasized that a single high BMR in itself does not establish a diagnosis. Several determinations should be obtained on different occasions and clinical findings must be given the careful consideration they deserve. Although the protein-bound (hormonal) iodine in the blood appears to provide a good index of thyroid activity, its determination is at present impractical for routine use.

The recent discovery of antithyroid drugs has reopened the whole question of medical versus surgical therapy of hyperthyroidism. During the past 25 years, thyroidectomy after pre-operative iodine preparation has enjoyed universal favor. Unfortunately, however, iodine has usually been frowned upon for prolonged medical use. This feeling is based upon the erroneous idea that patients "escape" from the drug. There is now fairly good agreement, however, that an apparent escape represents nothing more than the progress of a rising cycle of the disease, but still at a lower level than if iodine had not been given. In certain mild or questionable cases of hyperthyroidism, prolonged iodine therapy remains of distinct value. After several months' medication, these cases often experience a sustained remission.

The new antithyroid drugs which have enjoyed the widest clinical use are thiouracil, propylthiouracil and thiourea. These drugs by direct action on the thyroid cells prevent the synthesis of thyroid hormone. They do not abolish the goiter, but on the contrary promote hyperplasia and increased vascularity of the gland. This stimulation is purely anatomic and is mediated through the anterior pituitary. There is little or no gross increase in the size of the gland, however.

The antithyroid drugs are highly efficacious. Iodine usually only ameliorates the disease and does not provide complete control. The newer drugs, on the other hand, bring about complete remission in 95 per cent or more of cases within one to three months after institution of therapy. If continued from six to

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twelve months, approximately 60 per cent of cases remain in relatively permanent remission after withdrawal of the drug.

In view of the requisite lengthy treatment and frequent relapse there is considerable opinion favoring use of the drugs only in pre-operative preparation.<sup>1</sup> The more complete control of hypermetabolism renders the patient less susceptible to the hazards of surgery. Ideal preparation requires at least six weeks and iodine should be given concurrently during the last two to three weeks in order to reduce the hyperplasia and vascularity which would make the operative technic difficult. There is actually no objection to giving iodine simultaneously from the start inasmuch as recent evidence indicates that it enhances the action of the drug.<sup>2</sup>

One cannot at present draw final conclusions as to the status of the new drugs in therapy. Thiouracil is toxic.<sup>3</sup> Two and one half per cent of cases develop agranulocytosis, often with explosive suddenness and at any time from one week to a year or more after initiation of treatment. Four-tenths per cent of those

receiving the drug have died with this complication. Another 12 per cent of cases develop less serious complications, of which drug fever is the most common. Preliminary trials with propylthiouracil indicate that this drug is much less toxic than its parent.<sup>1</sup> Thio-urea, one of the first drugs used, also seems to be relatively safe and effective in doses of 0.1 to 0.3 Gm. daily.<sup>2</sup>

Radioactive iodine should be mentioned. The mechanism of action is identical with that of x-ray, but the difference lies in the high order of radiation applied directly to the cells—in fact, within the cell itself. Treatment has been successful in the limited number of cases tried, but it is too early to appraise the ultimate usefulness of the method. This therapy differs from other "medical treatment" in that thyroid cells are actually destroyed and the goiter is made to shrink.

### PARATHYROID

**Hypofunction.** The clinical findings consist of tetany and paresthesias of the extremities. Serum calcium is low and phosphorus is high. It should be remembered that similar blood changes may occur in kidney disease and rickets. Parathyroid hormone is of little use for maintenance of patients because of the development of resistance. In acute tetany intravenous calcium salts are very effective, and for maintenance good control can usually be achieved with 15 Gm. of calcium chloride daily, by mouth. The calcium may be supplemented if necessary with 0.5 to 2 cc. of dihydrotachysterol or 50,000 to 150,000 units of vitamin D.

**Hyperfunction.** The cardinal findings are high serum calcium, low phosphorus, high alkaline phosphatase and usually a characteristic demineralization of bones. It is well recognized, however, that a similar picture may be produced by generalized osseous neoplastic metastases. High serum calcium and demineralization of bone may also occur after immobilization of an extremity for fracture. The cause of hyperparathyroidism is usually a parathyroid tumor which is easily removed surgically.

### ADRENAL MEDULLA

**Hypofunction.** There is no known disorder due to hypofunction.

**Hyperfunction.** Hyperfunction occurs in the presence of a tumor (pheochromocytoma) which secretes excessive quantities of epinephrine. The disorder is typically characterized by paroxysms of hypertension, often accompanied by tachycardia, tremor, sweating

TABLE 1  
*Treatment of Choice in Hyperthyroidism\**

TYPE OF CASE	THIOURACIL	A "PERFECT" NONTOXIC DRUG
Mild	<i>Do not use.</i> Risk too great. Better treated with (1) iodine followed by surgery, or (2) iodine alone.	<i>Good treatment.</i> Attempt to induce medical remission. If relapse occurs, operate.
Moderate to moderately severe	<i>Do not use.</i> In straight medical therapy risk is as great as surgery. If used as pre-operative drug operative risk is not reduced enough to make up for hazard of toxicity. Better treated by surgery preceded by iodine.	As above
Extremely severe cases and iodine-resistant cases	<i>Use is justifiable</i> in preparation for surgery or possibly for maintenance.	As above
Cases complicated by disorders which increase surgical hazard (cardiacs, etc.)	<i>Use is justifiable.</i> Many cases should be maintained medically.	Continued medical maintenance is the treatment of choice.

\* The presence of nodular goiter (toxic adenoma) would in many cases shift the emphasis to surgical removal, particularly when there are mechanical effects from the growth. One cannot as yet say that a perfect drug exists. Propylthiouracil and thiourea in small dosage show promise.

and nervousness. Between attacks the patient is asymptomatic. A recent diagnostic test employs the intravenous injection of histamine.<sup>5</sup> A pyelogram usually reveals a displaced kidney, however, perirenal air injection is usually required to visualize the tumor itself. The latter procedure is not without hazard. After surgical resection of the tumor it is necessary to administer large doses of epinephrine to combat the shock-like fall in blood pressure. Fifty cubic centimeters of epinephrine in saline by continuous drip may sometimes be required in the first 24 hours.

### ADRENAL CORTEX

**Hypofunction.** A diagnosis of Addison's disease usually may be made by the typical clinical findings of pigmentation, asthenia, anorexia, weight loss and low blood pressure. When the condition progresses to crisis, there is dehydration, vomiting, fall in serum sodium and chloride and rise in the blood urea and nonprotein nitrogen. A safe diagnostic test which is almost invariably positive is the "water test."<sup>6</sup> It should be remembered, however, that nonspecific chronic wasting diseases and renal malfunction may give falsely positive results. The chloride excretion test<sup>7</sup> is fairly specific for Addison's disease, although its use is attended with the danger of provoking crisis. Patients undergoing it should be watched for weakness, anorexia, nausea and vomiting, the onset of which demands termination of the test in favor of vigorous treatment with saline and cortical hormone. Although 17-ketosteroid excretion is low in Addison's disease, such a finding is by no means specific.

Patients are best maintained by implantation of desoxycorticosterone pellets.<sup>8</sup> In the presence of stress such as a serious infection, additional vigorous therapy is required in the form of *crude cortical extract* (50 to 100 cc. daily). Hypoglycemia must be combatted with parenteral glucose, and saline should be given as necessary to restore any deficit in body water and electrolytes.

**Hyperfunction.** Either a tumor or hyperplasia of the gland may lead to hypersecretion. There are, moreover, two physiologic categories of hyperfunction. In one instance, the hormonal material is of a masculinizing type and the clinical consequences in the female include virilism with enlarged clitoris, male hair distribution, deep voice and amenorrhea. In the young boy a premature pseudopuberty appears. A 17-ketosteroid determination is of great value in diagnosis. Values are increased from 5 to 50 times above normal. Therapy is surgical if a tumor is demonstrated.

Cushing's syndrome, which results from the other

type of hyperfunction, is characterized, not by true obesity, but by a red, bloated face, protuberant abdomen, slender extremities, purple striae and asthenia. In the female there is usually amenorrhea and mild hirsutism. The 17-ketosteroids may be normal or moderately elevated. If the cause lies in a tumor, surgery is curative. In the absence of a tumor fair results have sometimes been obtained by radiation of the pituitary. This procedure is based on the assumption that a basophile tumor or hyperfunction of the anterior lobe may be exciting the adrenal to hyperfunction. Testosterone propionate in large doses has been employed with some success in order to reverse the negative nitrogen balance which is thought to be responsible for many of the clinical derangements.

### ANTERIOR PITUITARY

**Hypofunction.** Complete pituitary failure is associated with total loss of gonadal function, very low thyroid function, and sometimes a depression of the adrenal cortex so severe that Addison's disease is the presenting disorder. During childhood dwarfing is present. Patients with pituitary failure often do not suffer from the cachectic state described by Simmonds, whose cases were discovered among autopsy material. Wasting is actually not the most characteristic early feature of the disease. The "teen-age" girl presenting extreme weight loss, amenorrhea and a low metabolism is most likely suffering from anorexia nervosa and will respond to an adequate diet. True hypopituitarism is usually due either to a chromophobe tumor or a postpartum necrosis of the gland. Of help in diagnosis are determinations of 17-ketosteroids and gonadotropic hormone in the urine. Both are extremely low or absent.

It is debatable whether partial pituitary failure exists as a clinical entity. Perhaps some cases of amenorrhea are due to a "sluggish pituitary." Until practical methods are devised for precise evaluation of the multitude of pituitary functions the full answer will not be known.

It should be emphasized that hypopituitarism does not produce obesity. Some cases of supposed adipogenital dystrophy are simply fat boys with a penis which is not infantile but simply hidden in an overhanging suprapubic fat pad. Other cases may represent a combination of hypothalamic obesity plus some degree of pituitary failure which causes dwarfing and hypogonadism. Most cases under suspicion, however, if left alone will attain spontaneous sexual maturity by the age 16.<sup>9</sup> In some instances the endocrine mechanism is difficult to elucidate and a decision must be made, in each case, whether to give gonadotropin

or male hormone therapy. The obesity responds to diet and not to hormone injections.

**Hyperfunction.** The classical examples of hyperpituitarism are acromegaly and gigantism. The former may often be controlled by radiation of the offending eosinophilic tumor. If vision is ultimately threatened by optic compression surgical removal is justified. Basophilic adenomas of the pituitary exist and in some cases are associated with Cushing's syndrome. Their effect is thought to be indirect by stimulation of the adrenal cortex. They are rarely large enough to erode the sella.

### POSTERIOR PITUITARY

**Hypofunction.** Loss of function may result either from destruction of the lobe itself or the nerve tracts which connect the gland with the supra-optic nuclei. The resulting disorder is diabetes insipidus. Psychogenic polydipsia may lead to diagnostic confusion. In the latter condition, the high output of dilute urine is simply the result of excessive drinking of water. In frank diabetes insipidus water deprivation for 12 hours or more results in extreme thirst, often with dehydration, and the specific gravity of the urine does not rise above 1.010. It has been reported that the two conditions may be differentiated by a difference in response to hypertonic saline.<sup>10</sup>

The treatment of choice is pitressin tannate in oil.

**Hyperfunction.** There is no recognized clinical entity due to hyperfunction.

### OVARY

**Hypofunction.** Various degrees of ovarian dysfunction as related to menstrual disorders and sterility are beyond the scope of this discussion. In complete ovarian failure the most important deficiency is that of the follicular hormone—estrogen. When the condition occurs in young girls puberty does not occur. The menopause is due to primary ovarian failure. Low estrogen production is associated with a rise in gonadotropin production by the pituitary. The latter phenomenon is of diagnostic importance in that increased quantities of gonadotropin may be demonstrated in the urine by bio-assay.

Replacement therapy with estrogen is effective in ovarian failure. The question as to whether the menopausal state requires treatment must be answered separately for each patient. If symptoms consist only of mild flashes these usually pass away in a few months without therapy. If, however, flashes are severe and are accompanied by nervousness, insomnia, headache or dizziness it is well to give hormone. An attempt is then made to interrupt therapy at intervals

and decrease the dose until the estrogen may finally be entirely withheld.

There are those who fear that estrogen administration may lead to cancer. At the present time there is no good evidence that estrogen as used clinically will initiate a cancerous growth. It is likely, however, that if a cancer once arises in the breast or uterus such therapy will stimulate its growth and is therefore contraindicated.

Estrogenic preparations are available on the market in wide variety. Although the old ovarian extracts and desiccated ovarian materials are completely inert, some 60-odd preparations remain on the market. The newer synthetic products are particularly suitable for oral therapy. Their physiologic action is in every way comparable to that of the natural compounds although in some cases nausea is experienced. This symptom is not circumvented by parenteral injection but may usually be prevented by increasing the dose slowly from initially low levels. Complications of estrogen therapy (in any form), if dosage is too high, include uterine bleeding and sore breasts. These effects are due to excessive stimulation and are usually alleviated by a reduction in the dosage. Data concerning the more commonly used estrogens are included in Table 2.

**Hyperfunction.** An undisputed example of hyperfunction is that attending granulosa cell or theca cell tumors. The estrogen elaborated by these tumors causes uterine stimulation with bleeding, and in the immature girl breast development occurs. Arrhenoblastoma of the ovary is a rare tumor which secretes a masculinizing type of hormone.

### TESTIS

**Hypofunction.** If the onset of testicular failure antedates puberty there is failure of normal development of the penis, prostate, beard and voice. Muscles are poorly developed and the hips may be somewhat prominent. Marked obesity, however, is not a feature, but on the contrary the body is usually lanky with very long extremities. Contrary to common notion, sex interest, and power of erection and orgasm are often present, although seminal fluid is absent. Homosexual interest is not produced by hypogonadism.

Castration after puberty usually is followed by hot flashes, loss of strength, weight loss and nervousness. Facial hair is fairly well retained and the voice remains masculine. In a small percentage of men past middle life, there occurs a decline in secretion of male hormone (male climacteric). Symptoms are similar to those of the female menopause, although hot flashes

TABLE 2  
*Estrogens in Common Clinical Use*

CHEMICAL NAME	TRADE NAMES	SOURCE	COMMON TYPE OF PREPARATION	HOW ADMINISTERED	AVERAGE DOSE	PROBABLE DURATION OF ACTION	NAUSEA
Estrone	Estrone, Theelin	Urine	In oil	Intramusc.	1 to 2 mg.*	4 to 5 days	No
			Aqueous suspension	Intramusc. or subcutan.	1 to 2 mg.*	5 to 7 days	No
Mixture of estrone and related compounds	Amniotin, Estrogenic hormone, Estrogenic substance	Urine	In oil	Intramusc.	1 to 2 mg. of estrone equivalent	4 to 5 days	No
Estradiol benzoate	Ben-Ovocycin, Dimenformon benzoate, Progyon—B	Chemical treatment of estrone	In oil	Intramusc.	1/6 to 1/3 mg.†	5 to 7 days	No
Estradiol dipropionate	Di-Ovocycin Dimenformon dipropionate, Progyon—DP	Chemical treatment of estrone	In oil	Intramusc.	1 to 2.5 mg.	10 to 14 days	No
Ethinyl estradiol	Estinyl, Lynoral	Chemical treatment of estradiol	Tablets	Oral	0.02 to 0.04 mg.	1 to 2 days	Infrequent
Sodium estrone sulfate	Premarin	Urine	Tablets	Oral	1.25 to 2.5 mg.	1 to 2 days	Rare
Diethylstilbestrol	Diethylstilbestrol, Stilbestrol	Synthetic	Tablets	Oral	0.2 to 0.5 mg.	1 to 2 days	10% to 15% of patients
2,4-di( <i>p</i> -hydroxyphenyl) 3-ethyl hexane	Benzestrol	Synthetic	Tablets	Oral	2 to 3 mg.	1 to 2 days	Infrequent

\* 1 mg. of Estrone  $\approx$  10,000 International Units.† 1 mg. of Estradiol Benzoate  $\approx$  6,000 Rat Units.

may not be so prominent, while loss of strength and energy may be severe. Impotence is a variable accompaniment. Diagnosis may be confirmed by therapeutic trial with male hormone for two to three weeks (due allowance being made for the element of suggestion).

Therapy of male hormone deficiency is by the administration of testosterone propionate, 25 mg. by injection, two to three times weekly; methyl testosterone, 10 mg. three to four times daily by mouth; or pellet implantation of testosterone (usually six 75 mg. pellets). The latter are effective for three to four months.

**Hyperfunction.** A rare tumor of the interstitial cells causes premature masculinization when it occurs before puberty.

## BIBLIOGRAPHY

- Means, J. H.: *Ann. Int. Med.*, 25:403, 1946.
- Danowski, T. S., E. B. Man, and A. W. Winkler: *J. Clin. Investigation*, 25:597, 1946.
- Van Winkle, W., Jr., S. M. Hardy, G. R. Hazel, D. C. Hines, H. S. Newcomer, E. A. Sharp, and W. N. Sisk: *J. A. M. A.*, 130:343, 1946.
- Astwood, E. B., and W. P. Van der Laan: *Ann. Int. Med.*, 25:813, 1946.
- Roth, G. M., and W. F. Kvale: *Am. J. M. Sc.*, 210:653, 1945.
- Kepler, E. J., and D. M. Willson: *Arch. Int. Med.*, 68: 979, 1941.
- Cutler, H. H., M. H. Power, and R. M. Wilder: *J. A. M. A.*, 111:117, 1938.
- Shipley, R. A.: *Am. J. M. Sc.*, 207:19, 1944.
- Werner, S. C.: *J. Clin. End.*, 1:134, 1941.
- Hickey, R. C., and K. Hare: *J. Clin. Investigation*, 23: 768, 1944.

# Conduction Anesthesia for Focal Neuralgias in Rhinologic Practice

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PHILADELPHIA, PENNSYLVANIA

The frequency with which patients with facial neuralgias appear for relief in the office of the rhinologist indicates the importance of the question to the practitioner in this field. The patient often comes asking for a plastic operation, but on careful examination this procedure is found not to be indicated. Patients frequently may feel sure that they have sinus infection, but examination shows this to be a mistaken idea. The area most commonly involved is about the brow and forehead, only somewhat less often, the pain is in the nasociliary region.

The importance of this subject is worthy of emphasis not only in behalf of the patient, who is suffering pain, but of the rhinologist, who must relieve him. Teeth are often extracted needlessly, and tonsils are removed unnecessarily. Sinus operations and antrum punctures, too, are done blindly, none giving relief for this type of complaint. The patient endures the wear of continued discomfort, both from the original pain and the mistaken measures, which fail to cure.

The *complaint* is variously described, by some as a pain that is sharp and shooting, by others as a pain like a toothache, and again suggesting the pain caused by an electric current. Sometimes the pain is described as radiating. The duration is short and usually comes on with brief intervals of relief. The pain does not necessarily occur every day, nor with predictable regularity.

Patients with these types of pain may be loosely grouped, as follows:

1. Neuralgia without demonstrable intranasal pathology.

CASE I. Female, age 52 years. She complained of severe shooting pains over the right eye, radiating behind the ear, over the forehead and in the occipital region. The pain was intermittent and made worse by changing the position of the head. She had already been treated by several different physicians without relief, and a final diagnosis of migraine had been made. A complete general physical examination was done, including special study of the regions about the nose and also about the eyes. Injection treatment gave relief and the head position could be changed without discomfort.

2. Neuralgia with sinus involvement.

CASE II. Female, age 38 years. The patient complained of severe, more or less constant, headache with shooting pains over the left eye, radiating to the left temporal region and ear. Nausea and vomiting accompanied this pain. Transillumination showed a cloudy left antrum and the maxillary antrum was found cloudy on x-ray examination. All pains disappeared on clearing up the infections.

3. Neuralgia associated with rhinitis and ethmoiditis.

Neuralgia is a common symptom of acute rhinitis, and is present in many cases of ethmoiditis and sphenoiditis. This group of patients is much the largest of those having neuralgia. Curing the nasal and sinus conditions relieves all symptoms.

4. Neuralgia, a symptom complex associated with a general pathologic condition, not directly related to the nose.

CASE III. A patient with severe head pains, localized over both supra-orbital regions, presented no nasal disease on careful study, but had a positive Wassermann test. Relief followed adequate antiluetic treatment.

5. Neuralgia in a group presenting faults of nasal anatomy.

CASE IV. Male, age 22 years. He had been hit with a baseball bat two years before. There had been no trouble after the first effects of the blow had passed. After two years, however, he began to have pain over the right supra-orbital region and the cheek. X-ray showed an old fracture of the right malar bone. Although this could not be conclusively demonstrated, it seemed probable that narrowing of the foramen had resulted from the injury, with consequent pressure on the nerve. Novocaine injection gave only temporary relief, and was followed by a phenol-alcohol injection with permanent cure.

6. Neuralgia with psychogenic factors.

CASE V. Male, age 49 years. Complained of "terrific" pains in the right supra-orbital and nasociliary regions, the latter centering at the right inner canthus. He gave a history of having blown blood from the right nostril for the past eight years. Examination revealed polyps in the right middle meatus and hyperplastic change of the middle turbinate. Operative removal of all the diseased parts gave

no relief from the pain. The surgical material was submitted for pathologic examination and was reported to be simple polyp tissue. The patient appeared at the office to hear the pathology report, with tears running down his face and complaining of "terrific" pain. On hearing the diagnosis of simple polyps, his pain subsided at once. He had been reading about cancer and was sure that he was a victim of the disease. At the last interview, three years later he was still free from pain.

The symptoms in neuralgia may also resemble those of migraine, though they do not respond to the specific treatment for this condition.

The pain may be precipitated by washing the face, by talking, chewing, exposing the face suddenly to cold air, and some complain that it can come from the pressure of spectacles on the nose. Pain may be intensified by a change in position of the head, as in bending forward or downward and even by the change of temperature as in going from one room to another.

Of these several groups, the type to be primarily considered here is the first, in which the neuralgia is the only finding. As has been shown in the group classification, neuralgic pain may accompany a variety of conditions, in which pain can be relieved temporarily, until operative treatment is possible.

### DIAGNOSIS

After carefully ruling out any organic diseases, a considerable group of cases remains with no demonstrable cause for the pain. A general localization can be indicated by the patient, but a more exact focus can be detected by repeated pressure, especially at the points of nerve exit from the bony skull. The writer does this by means of the rubber eraser on a pencil. In this way pressure can be exerted evenly and in a suitable degree to elicit a reaction to tenderness or pain. Treatment is administered at these points.

### TREATMENT

The most frequent site of pain is at the supra-orbital notch. With the usual surgical preparation, the nerve is injected with 1 per cent novocaine and 1:20,000 adrenalin. This procedure gives immediate relief of the pain.

The point which is second in frequency in facial pain is associated with the nasociliary nerve. The exact place for injection is at the junction of the nasal bone with the upper lateral cartilage at about the midpoint.

Less frequently, pain can be relieved by injection of the sphenopalatine ganglion. The point of entrance is determined by drawing a horizontal line outward from and parallel to the lower surface of the external

nose; a second line is dropped perpendicularly from the external canthus of the eye, at right angles to the first one. A needle 7 cm. long is entered at this point of junction of the two lines, and is extended backward, medially and slightly downward to reach the pterygo-maxillary fossa, where 3 to 5 cc. of novocaine are injected.

Occasionally the postauricular nerve is involved and injection is done behind the ear near the occiput.

If the relief given by this treatment is only temporary, then the injections are repeated using 50 per cent alcohol, which usually gives permanent results.

### DISCUSSION

The symptom in all of these cases is recurrent pain, and the source of the pain is chiefly the fifth nerve, through its terminal branches.

**Anatomy.** The sensory root fibers of the fifth (trigeminal) nerve arise from the cells in the gasserian (semilunar) ganglion. This ganglion lies on the petrous portion of the temporal bone, near its apex, and in the dura mater. It is of interest that small branches are given off to the cerebellar tentorium and to the dura mater of the middle cranial fossa. It is also of interest, that the ganglion receives filaments from the carotid plexus of the sympathetic system.

The gasserian ganglion gives rise to three branches:

1. The ophthalmic, with its associated small ciliary ganglion.
2. The maxillary, connected with the sphenopalatine ganglion.
3. The mandibular with the communicating small otic and submaxillary ganglions. All of these small accessory ganglions receive sensory filaments from the trigeminal nerve and various autonomic fibers also.

The ophthalmic division is the sensory nerve of the eyelid, eyebrow, forehead and nose; also, part of the nasal mucous membrane and some of the paranasal sinuses. Filaments from the cavernous plexus of the sympathetic join this nerve. Just before entering into the orbit, this branch divides into three parts: (1) lacrimal, (2) frontal, (3) nasociliary. The frontal, the largest branch and a continuation of the ophthalmic itself, enters the orbit through the superior orbital fissure and lies directly upon the periosteum as it runs forward under the levator palpebrae superioris. Midway between the apex and the base of the orbit, the frontal divides into: (1) supratrochlear, which supplies the skin of the lower part of the forehead and a part of the upper eyelid; (2) the supra-orbital, which passes

through the supra-orbital foramen, where it gives off filaments to the upper lid, then upward to the forehead, where it ends in a medial and a lateral branch to supply the integument of the scalp. Both branches also send small fibers to the pericranium.

The nasociliary branch is smaller than the frontal, but larger than the lacrimal and enters the orbit to run obliquely to the medial wall of the cavity. It then enters the cranial cavity through the anterior ethmoidal foramen where it passes through a shallow groove on the lateral margin of the cribriform plate of the ethmoid, and runs downwards into the nasal cavity through a slit at the side of the crista galli. Its terminal filaments supply the mucous membrane of the anterior septum and of the lateral cavity walls. It reaches the external surface of the nose between the lower border of the nasal bone and the lateral nasal cartilage, to supply the skin of the nose below this line. The ciliary portion is made up of branches from the ciliary ganglion which go to the eyelids and the side of the face, and to the ethmoidal and sphenoidal sinuses.

The maxillary nerve sends branches to (1) the eyelid (palpebral); (2) the skin of the side of the nose (nasal); (3) the upper lip (labial).

Other areas about the head which are seats of neuralgic pain are supplied by the upper cervical nerves. The medial branch of the 2nd cervical (great occipital nerve) is the main cutaneous nerve for the posterior part of the scalp as far forward as the vertex. The great auricular nerve arises jointly from the 2nd and 3rd cervical to supply the skin over the mastoid process and much of the ear, the skin of the face over the lower part of the masseter muscle and in front of the ear.

**Physiology.** This complex of nerve fibers serves a sensory function, including those branches from the autonomic system. Touch, temperature (both heat and cold) and pain are thus conducted by this network, both from direct and reflex stimulation. There are many focal areas where endogenous stimuli may arise: Notably, where the nerves or their ganglions are surrounded by intracranial membranes (dural); where they pass through bony canals and foramina, and also under abnormal surrounding conditions from the pressure of their own connective tissue sheaths. Sufficient pressure at any one or more of these localities can cause pain. The skin has been said to be the most sensitive tissue in the body. Pain may also arise in the connective tissue of muscle, and from the periosteum where there are numerous nerve filaments.

The effect of focal spasm of the vasomotor nerves (autonomic) has been discussed both for and against,

in relation to these neuralgias. The sympathetic supply, which is associated with the trigeminal nerve, would seem to justify the consideration of this source of pain. Demonstration of pain reaction in blood vessels has been thoroughly demonstrated, and reported.

**Pain.** This sensation is difficult to define, since it is subjective and must be interpreted by the person who experiences it. Sherrington defines pain as "the psychical adjunct of an imperative protective reflex." Both the physician and the patient might prefer to agree that the word pain cannot be defined satisfactorily since it is known only by experience and can be described only by illustration, as being "like" something else. Its meaning is very general and inclusive.

The question of whether pain is a protective reflex has been questioned, on the ground that pain often occurs in consciousness only as a late phenomenon and so is not protective. Since the observation still holds, that literally "the burnt child fears the fire," there are conditions where it is unquestionably protective. But it has also been said that pain may pass beyond the protective stage and become destructive, since pain if long continued interferences with the processes of thinking, it disturbs sleep, upsets the appetite for food, and it may go so far as to disturb body functions even more seriously. It may even lead to attempts at suicide, as has been observed in this writer's professional experience.

The question of differentiating *neuralgia* and *neuritis* can be answered by the fact that neuritis connotes an inflammatory process in a nerve, or a causal factor, while neuralgia (pain) is an effect, a symptom either of an inflammation or of some of the many other stimuli capable of harming the organism.

The source of the pain under consideration here involves primarily the trigeminal (5th cranial) nerve, as has been indicated, though its manifestations are only through its terminal branches. Signs of ganglion involvement are lacking, which differentiates the condition from the true trigeminal neuralgias, and from Sluder's syndrome, which may be simulated.

In the more obscure cases, the psychic factor should be particularly kept in mind. Cushing described a case of a young woman of 35 years, who complained for a number of years of an almost incessant pain which seemed to localize mainly in the left upper bicuspid tooth. The pain then spread to the left face, ear and shoulder. Teeth were extracted, the alveolar arch was curetted; an infra-orbital neurectomy was done; also deep alcoholic injections were made with no relief. Then there was a total avulsion of the trigeminal nerve root, but pain persisted. Injection of the sphenopalatine ganglion was without effect. Fi-



nally, there was surgical removal of the ganglion itself—but still the pain remained with varying degrees of intensity.

Cushing also gave the reminder that there is no satisfaction to the physician in the use of the terms hysteria, pseudoneuralgia or psychalgia, since the mechanism of none of these is known, and they offer no relief to the patient.

## SUMMARY

Conduction anesthesia by the injection of novocaine can be used for temporary relief of focal pain where lesions about the nose are demonstrable. By the injection of novocaine, followed by alcohol if necessary, one can secure permanent relief from intractable pain which is focal, but without demonstrable cause.

*2104 Spruce Street*

# BOOK REVIEW . . .

**DIAGNOSIS AND TREATMENT OF ACUTE MEDICAL DISORDERS.** By Francis D. Murphy, M.D. Second edition. 546 pages. Philadelphia, F. A. Davis Co., 1946. \$6.50.

Dr. Murphy is well fitted, from years of experience as Clinical Director of the Milwaukee County General Hospital, to write a book of this type. To be sure much of what is contained in this volume can be found in the several commonly used textbooks of medicine. However, the author approaches the diseases from a different angle than the usual presentation in texts on medicine. Dr. Murphy is interested here in discussing acute disease and medical emergencies. Thus little space is given to a discussion of etiology and pathology, but much emphasis is placed upon diagnosis and treatment. This approach makes it a valuable reference text for the general practitioner.

Obviously it will be impossible to mention all the medical emergencies discussed in the book. But the reviewer will try to indicate something of its content.

Among the diseases of the blood are good presentations of the several acute leukemias, the purpuras and agranulocytosis. All hematologists would not agree that splenectomy is specific in essential thrombocytopenic purpura. The reviewer feels that a discussion of Banti's disease should include some of the newer concepts regarding congestive splenomegaly.

Under vascular disease the consideration of the treatment of thrombophlebitis and acute arterial occlusion is good. Therapy of shock is well covered. The reviewer questions the efficacy of the use of hormones in preventing hypertensive cerebral vascular crises. The diagnosis of angina pectoris and coronary occlusion are adequately covered, especially the differential diagnosis of the latter. The management of these two conditions is presented in detail. The same

is true of the treatment of failure of both the left and of the right heart. Outlines of diagnosis and treatment of the several cardiac arrhythmias, endocarditis and pericarditis complete the cardiovascular section of the book.

The treatment as given for diabetic coma is quite good as is its differential diagnosis from insulin reactions and cerebral accidents. Fortunately the use of thiouracil in thyrotoxicosis is presented in a conservative manner. The treatment outline for crises in Addison's disease is excellent.

Under the section on the nervous system appears a discussion of diagnosis in the presence of coma and also of convulsions, and diagnosis and management of cerebral accidents of various types. The diagnosis and management of acute nephritis, uremia and renal colic are the major subjects for consideration under the section on renal disease.

The pneumonias, acute asthma, pneumothorax, military tuberculosis and emergencies such as massive collapse, foreign body and hemoptysis are included in the discussion of acute pulmonary disorders. In addition to the usual abdominal emergencies of surgical interest Dr. Murphy includes ulcerative colitis, a consideration of jaundice and acute yellow atrophy.

Several chapters are devoted to a consideration of acute infectious diseases of nontropical and tropical distribution. Lastly there is a good chapter on the toxicology and treatment of acute chemical and drug poisoning.

Though the reviewer and others may not agree in all respects with the treatment outlined for acute medical disorders, this does not detract from the value of this book as a reference work in the field indicated by its title. Therefore this volume is recommended especially for the general practitioner of medicine.

R. H. K.

*The author discusses the etiology of portal cirrhosis and the mechanisms causing the symptoms and signs of the disease. His presentation of treatment is based upon the newer knowledge of the causes of this disease.*

## The Pathologic Physiology of Portal Cirrhosis\*

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Cirrhosis has been defined as a diffuse scarring of liver which has followed destruction of liver, and which is accompanied by a widespread regeneration of liver substance.<sup>1</sup> This rather unique situation of fibrotic repair and extensive regeneration explains many of the clinical situations that occur in the course of this syndrome.

### THE ANATOMY OF THE LIVER WITH RESPECT TO CIRRHOSIS

Each liver lobule is made up of a central vein surrounded by radiating cords of liver cells and, at the periphery of the lobule, the portal triad made up of the portal vein, the hepatic artery, and the bile canaliculus. It is important to recognize that the area about the central vein is the most vulnerable area of the liver. Indeed, central necrosis of the liver, i.e., degeneration of hepatic parenchyma about the central vein is often the first sign of hepatic damage. The reason for this is not clear, but it has been suggested that inasmuch as the area about the central vein is the area farthest from the oxygen supply brought via the hepatic artery, this is the most vulnerable area within the liver.

The liver receives a dual blood supply, part of which comes by way of the hepatic artery. This blood, about one-seventh of the total hepatic blood supply, is relatively rich in oxygen and under a relatively high head of pressure. A greater volume of blood by far, about six-sevenths of the hepatic blood supply, is brought to the liver via the portal vein. The portal blood supply arrives in the liver after it has already passed through one capillary bed; it is relatively low in oxygen tension and arrives at the liver with a low head of pressure. Both the hepatic

arterial supply and the portal venous supply are vital for normal liver function. Following abrupt occlusion of the hepatic arterial supply, infarction of the liver develops. On the other hand, following abrupt occlusion of the portal blood supply, acute hepatic insufficiency invariably occurs. When experimentally the portal blood supply is gradually shunted away from the liver to prevent the development of acute hepatic insufficiency, the liver atrophies to about one-third its previous size.

In cirrhosis of the liver with chronic scarring and obliteration of the portal circulation, the portal blood supply gradually is shunted away from the liver and into collateral channels. McIndoe<sup>2</sup> has demonstrated by a series of beautiful reconstructions the gross distortion of the hepatic portal circulation that is found in the presence of portal cirrhosis. There is a very marked reduction in the portal circulation through the liver and this is associated with the development of atrophy of the liver. In the presence of cirrhosis of the liver with complete distortion of the normal portal-hepatic vein pattern, only about one-third of the blood transfused through liver enters the hepatic vein. The remainder of the blood supplied to the liver arriving from the portal circulation is shunted into collateral channels. The obstruction to the portal circulation in cirrhosis and subsequent atrophy of the liver results in an increase in pressure in the portal circulation because of the obstruction within the liver to the outflow of portal blood. To compensate for this obstruction within the liver, various anastomotic channels develop. Esophageal varices, a caput medusae, and hemorrhoids characteristically follow obstruction to the portal circulation.

### THE ETIOLOGY OF CIRRHOSIS

From experimental evidence that has been carried out in several laboratories in recent years, it is known that experimental portal cirrhosis quite similar to clinical cirrhosis may be produced in a number of

\* From the School of Medicine of the University of Pittsburgh, Pittsburgh, Pa.

Lecture delivered for the American College of Physicians Post Graduate Course given by the School of Medicine of the University of Pittsburgh, September 1946.

different ways. It may be produced by a protein-deficient diet when this diet is persisted in for a considerable length of time, and it may be produced by diets which are deficient in the B complex vitamins.<sup>3,4</sup> Several noxious agents, notably carbon tetrachloride and other chlorinated hydrocarbons may produce a picture essentially similar to portal cirrhosis.<sup>5</sup> From a clinical point of view, alcohol is widely looked upon as a causative factor in cirrhosis. This is true despite the fact that experimentally it is difficult or impossible to produce cirrhosis in animals by the administration of alcohol alone. To produce experimental cirrhosis by the administration of alcohol other factors must be present such as dietary deficiencies in protein or the B complex vitamins or the addition not only of alcohol, but of one of the chlorinated hydrocarbons to the experimental program.

There is a good deal of evidence that in clinical cirrhosis, the ingestion of alcohol is not a primary causative factor, but rather is only an additional factor which coupled with a diet which is chronically depleted in B complex vitamins, causes cirrhosis to develop. In other words, the alcohol is not the primary factor, but contributes to the anorexia and to the dietary inadequacies and these are of prime importance in the development of so-called alcoholic cirrhosis.

Although cirrhosis occurs frequently in nonalcoholics such as those residing in India and Syria,<sup>6</sup> and although cirrhosis occurs six to seven times as often in alcoholics as it does in the general population,<sup>7</sup> there is actually a rather low incidence of cirrhosis among chronic users of alcohol.<sup>8</sup> Probably those individuals who drink constantly or episodically but who eat an adequate diet do not develop cirrhosis. On the other hand, those drinkers who eat an inadequate diet are quite likely to develop cirrhosis. It is important to note that during prohibition there was a sharp reduction in the number of deaths from cirrhosis, but following the repeal of prohibition, there has been a definite rise in the number of deaths from this cause.<sup>8</sup>

In addition to starvation and dietary deficiencies, there are other causes of clinical cirrhosis. Chronic biliary obstruction is likely to produce cirrhosis, evidently because of the chronic inflammation about the bile canaliculi.

Chronic or recurrent cardiac failure with chronic passive congestion within the liver also may cause cirrhosis. Cardiac cirrhosis is recognized only in individuals with longstanding cardiac failure and is unlikely to occur with cardiac failure of short duration.

Syphilis is also a cause of cirrhosis. It does this by gross destruction of liver tissue; this destruction is fol-

lowed by fibrotic repair and the characteristic regeneration of hepatic parenchyma.

Certain hepatotoxic agents already mentioned under experimental cirrhosis likewise may contribute to cirrhosis in the clinical situation. This is not commonly found, but chronic exposure to the chlorinated hydrocarbons and various other agents may produce cirrhosis. The extensive studies of Mallory<sup>9</sup> implicated copper as a causative factor in cirrhosis of the liver. It is yet too early to discuss the possible rôle of previous attacks of infectious hepatitis or homologous serum jaundice in the development of portal cirrhosis.

### SYMPTOMS

The symptoms of cirrhosis deserve some consideration because the symptoms of this disease are often not interpreted as being due to cirrhosis until late in the course of the disease. Individuals with cirrhosis may have few or no symptoms until severe hepatic damage has occurred. The reason for this is apparent when the tremendous reserve capacity of the liver is considered. The liver is able to carry on adequate function in the presence of destruction of a major portion of hepatic tissue. In the presence of adequate hepatic function, despite some damage, symptoms will not develop unless there is some side action or result of the hepatic damage which produces recognizable symptoms. Indeed, indigestion and a vague feeling of weakness, neither of these being specific or characteristic, may be the only symptoms in cirrhosis until relatively late.

Ascites is frequently the presenting symptom in cirrhosis of the liver. It has been estimated that 78 per cent of individuals with cirrhosis develop ascites.<sup>10</sup> Splenomegaly, a development that is due to the increased pressure in the portal system, is often the first clinical sign of developing cirrhosis. Seventy-nine per cent of individuals with cirrhosis of the liver are thought to have splenomegaly.<sup>8</sup> Not infrequently, gastro-intestinal hemorrhage is the first sign of cirrhosis. This, of course, is due to bleeding from the anastomotic channels about the obstructed portal circulation and may be a severe and uncontrollable clinical symptom.

Abdominal pain is not frequently a sign of cirrhosis in our experience unless there is a superimposed hepatitis. Jaundice, likewise, is a late sign of cirrhosis and is seen only in the presence of hepatitis. Peptic ulcer has been reported in over 19 per cent of individuals with cirrhosis.<sup>11</sup> This high incidence of peptic ulcer has been thought to be due to the interference with the normal supply of the alkaline bile salts.

Loss of libido and the characteristic male distribution of hair occurs frequently in cirrhosis of the liver. It is thought that the mechanism of this is the inability of the damaged liver to inactivate natural estrogens and, therefore, since the damaged liver is unable to inactivate estrogens, the male who normally has a certain amount of circulating estrogen substances develops some of the signs of estrogen administration. Failure of the damaged liver to adequately inactivate estrogen has recently been considered as influencing the development of cancer.<sup>12</sup>

### THE MECHANISM OF ASCITES

A few years ago it was felt that the ascites of cirrhosis was largely due to the combination of portal hypertension and hypoproteinemia. There is now, however, considerable evidence which tends to dispute these explanations as being the sole factors in the development of ascites. Ancel Keys<sup>13</sup> has recently studied protein-deficient diets in conscientious objectors and has found that edema may develop on a nutritional basis in the absence of significant decreases in plasma protein concentration. The reason some individuals have a critical edema level of plasma protein and in other individuals this does not seem to be evident is quite obscure. The viscosity of the plasma may be an important factor just as is the osmotic force exerted by the plasma protein. One of the reasons portal obstruction alone is not an adequate explanation of ascites is that with experimentally induced portal hypertension, ascites does not frequently occur. Evidently some factor in addition to the portal hypertension and the hypoproteinemia is necessary for the development of ascites. Bollman<sup>6</sup> in a series of experiments in animals with experimental biliary cirrhosis found that when these animals were placed on a diet high in protein they would develop ascites within 24 hours. However, as long as these same animals were maintained on a carbohydrate diet, they did not develop ascites. Apparently these animals with damaged hepatic function were unable to handle the protein foods adequately and ascites developed; however, the mechanism of this ascites is certainly not clear.

### DIAGNOSTIC MEASURES IN CIRRHOSIS

Probably the most important diagnostic measure in cirrhosis is to consider the possibility of the disease. In the absence of an enlarged, fatty liver or a hard scarred liver which by physical examination makes one suspect cirrhosis, there are certain laboratory tests which may give a particular lead. The single laboratory test which is most likely to be positive in

the presence of cirrhosis is bromsulfalein retention. In this test when a large dose of dye is given (5 mg. per kg. of body weight) and when the blood sample is drawn 45 minutes later with care to prevent hemolysis, most individuals with cirrhosis of the liver will show some retention of the dye. We feel that this is the best single test in individuals with suspected cirrhosis of the liver.

The cephalin-cholesterol flocculation reaction will be positive in cirrhosis, but only when there is active parenchymatous liver disease in addition to the fibrotic and regenerative lesions. The cephalin-cholesterol flocculation test depends upon the presence of some abnormal blood constituent, presumably an abnormal globulin, and this abnormal protein in the plasma is probably produced by an actively damaged liver. Liver cells which have been replaced by fibrotic tissue do not produce these abnormal substances. Therefore, the cephalin-cholesterol flocculation test, although it is a valuable test of hepatic function, is not necessarily positive except when there is accompanying the cirrhosis, active, parenchymatous liver disease. Occasionally, peritoneoscopy will provide the first or most definite diagnostic aid in cirrhosis, and when the diagnosis of cirrhosis is suspected and cannot be proved by other clinical means, peritoneoscopy is indicated.

### THE TREATMENT OF PORTAL CIRRHOSIS

It has been amply demonstrated that a high-protein, high-carbohydrate diet is a valuable agent in preventing liver damage. A diet which contains in addition to these factors, an adequate number of the B complex vitamins will enable animals to tolerate larger amounts of noxious agents. Therapeutic measures once cirrhosis has developed vary depending upon the stage of cirrhosis that is present. Early in cirrhosis of the liver before there has been gross fibrous tissue replacement of hepatic parenchyma, fatty infiltration of the liver occurs, the so-called hypertrophic stage of cirrhosis of the liver. In the hypertrophic stage of cirrhosis the lesion is definitely a reversible one and if adequate therapy can be provided during this stage of cirrhosis, the outlook is quite good for recovery or at least remission in the course of the disease.

The agents which are probably effective in combating fatty infiltration include the following: a high-protein, high-carbohydrate, low-fat diet; the B complex vitamins because they enable the liver to function with maximum possible efficiency; the lipotropic sulfur-containing amino acids such as methionine or the combination of choline and cysteine are probably

also of value. However, the administration of methionine or choline and cysteine, the combination of which can presumably yield methionine, to an individual who has been eating a normal diet, does not appreciably influence the resistance to hepatic disease or fatty infiltration. However, in the patient who has been on a deficient diet, as may be presumed in an individual who has the hypertrophic stage of cirrhosis, these agents may be effective as lipotropic substances. From a practical point of view, it is interesting to note that one gram of methionine is available in a quart of whole milk. High-carbohydrate diets may be as beneficial as high-protein diets; Bollman has indicated in a personal communication that there is a good deal of evidence that one can do as much with a high-carbohydrate regime as one can with a high-protein regime.

The administration of serum albumin, particularly salt-poor albumin, to combat the hypoproteinemia that goes with cirrhosis is, of course, largely limited to the services that have this substance available. The cost of salt-poor albumin for the average individual, unfortunately, does not make its administration feasible.

Tapping to relieve the ascites must be done at times. The ascites, however, is generally not seen until the liver has passed through the hypertrophic stage of cirrhosis and developed the atrophic stage.

Because a high percentage of individuals with cirrhosis of the liver die from the effects of the portal hypertension, certain surgical measures have been devised for the treatment of this disorder. It has been estimated that about one-third of the individuals dying of cirrhosis die as a result of hemorrhage and about two-thirds of the individuals dying with cirrhosis die from cholemia or hepatic failure.<sup>8</sup> The surgical approach to the treatment of cirrhosis and portal hypertension may be divided into five categories. First and probably of least importance is the injection of esophageal varices. By the injection of esophageal varices it is possible to sclerose them and to reduce the possibility of hemorrhage. However, this is a procedure requiring special skill and it does not attack the cause of the disorder, i.e., the portal hypertension.

The second surgical method of treating portal hypertension is coronary vein ligation. By ligation of the coronary vein of the stomach, it is, of course, possible to reduce the pressure in coronary varices, but this again does not lower the underlying portal hypertension.

The third surgical approach to the problem of cirrhosis and particularly in cirrhosis associated with splenomegaly is splenectomy. Splenectomy, because it reduces the portal blood flow, is occasionally an effective

means of relieving the portal hypertension in cirrhosis.

The fourth approach to this problem is operative procedures by which the portal hypertension is shunted into the vena caval system. One of these brought into prominence by Whipple<sup>14</sup> has been splenorenal anastomosis. In this procedure Whipple anastomoses the splenic vein with the left renal vein after removing the spleen and kidney. This shunts the high portal pressure into the vena caval system which is better able to tolerate the higher pressures. This procedure has the distinct disadvantage of sacrificing a kidney and the spleen.

Recently, since the development of Blakemore's<sup>15</sup> nonsuture technic for vascular anastomosis, direct portocaval anastomoses have been produced to bypass this portal hypertension, or rather to shunt the portal hypertension into the caval circuit. This has been carried out by the direct anastomosis of the portal vein with the vena cava. This procedure in the experimental animal reduces the portal blood flow and produces hepatic atrophy. In the presence of cirrhosis, portal obstruction exists and a portal shunt has already been established. Because of this, little of the portal blood flow is passing through the cirrhotic liver and, therefore, to completely shut the hepatic portal flow off and produce a surgical portocaval fistula does not abruptly decrease the hepatic portal blood flow. This is technically a difficult procedure and none of the surgical measures has been followed long enough to accurately evaluate the long-term results of surgical treatment.

With respect to the surgical treatment of the ascites, two procedures are currently utilized. One of these is ureteroperitoneal drainage. In this procedure after sacrifice of the kidney, a ureter is opened into the peritoneal cavity and in this way, the peritoneal cavity is constantly drained of its ascitic fluid. From a practical point of view this procedure is not very satisfactory. Recently a method was described for using a plastic or glass button to drain the ascitic fluid into the subcutaneous tissues.<sup>16</sup> This method has not yet been widely used but deserves some consideration.

#### BIBLIOGRAPHY

1. MacCallum, W. G.: *A Textbook of Pathology*, ed. 7, Philadelphia, Saunders, 1940.
2. McIndoe, A. H.: Vascular lesions of portal cirrhosis, *Arch. Path.*, 5:23 (Jan.) 1928.
3. Gyorgy, P.: Experimental hepatic injury, *Am. J. Clin. Path.*, 14:67 (Feb.) 1944.
4. Gyorgy, P., and H. Goldblatt: Hepatic injury on a nutritional basis in rats, *J. Exp. Med.*, 70:185 (Aug.) 1939.

5. Bollman, J. L., and F. C. Mann: Experimentally produced lesions of liver, *Ann. Int. Med.*, 5:699, 1931.
  6. Yenikomshian, H. A.: Non-alcoholic cirrhosis of the liver in Lebanon and Syria, *J. A. M. A.*, 103:660 (Sept.) 1934.
  7. Jolliffe, N., and E. M. Jellinek: Vitamin deficiencies and liver cirrhosis in alcoholism, *Quart. J. Study Alc.*, 2:544 (Dec.) 1941.
  8. Tumen, H. J.: Cirrhosis of the liver. In H. L. Bockus (Ed.): *Gastroenterology*, Philadelphia, Saunders, 1946, p. 297, Vol. III.
  9. Mallory, F. B.: Cirrhosis of the liver, *New England J. Med.*, 206:1231 (June 16) 1932.
  10. Ratnoff, O. D., and A. J. Patek, Jr.: The natural history of Laennec's cirrhosis of the liver, *Medicine*, 21:207 (Sept.) 1942.
  11. Schnitker, M. A., and G. M. Hass: A histologic study of the liver in patients affected with peptic ulcer, *Am. J. Digest. Dis.*, 1:537, 1934.
  12. Ayre, J. E., and W. A. Bauld: Thiamin deficiency and high estrogen findings in uterine cancer and in menorrhagia, *Science*, 103:441 (April 12) 1946.
  13. Keys, Ancel, H. L. Taylor, O. Mickelsen, and A. Neuschel: Famine edema and the mechanism of edema formation, *Science*, 103:669 (May 31) 1946.
  14. Whipple, A. O.: The problem of portal hypertension in relation to the hepatosplenopathies, *Ann. Surg.*, 122:449 (Oct.) 1945.
  15. Blakemore, A. H., and J. W. Lord: The technic of using vitallium tubes in establishing portacaval shunts for portal hypertension, *Ann. Surg.*, 122:476 (Oct.) 1945.
  16. Crosby, R. C., and E. A. Cooney: Surgical treatment of ascites, *New England J. Med.*, 235:581, 1946.
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### Is Cancer Caused by Mutation?

A cancer may not be, as commonly explained, a mass of the patient's own cells gone wild and growing anarchically. The diseased cells, although originally flesh of his flesh, may have in a dreadful sense become strangers to the body in which they dwell, through one of those sudden, leaping evolutionary changes known as mutations. Had such a change occurred in one of the reproductive cells, the resulting child (if it lived) would be a freak of some kind, unrecognizable as the offspring of its parent.

This lack of real genetic kinship between the patient's normal body-cells and the cells of his cancer may account, among other things, for the refusal of the cancer to obey the commands of the growth-regulating chemicals, or hormones, that keep the normal parts of the body properly disciplined.

Striking new evidence bearing on this theory was presented before the meeting of the National Academy of Sciences in Washington by Dr. M. Demerec, head of the genetics department of the Carnegie Institution of Washington. Dr. Demerec has succeeded in producing mutations in fruitflies, classic experimental material of geneticists, by exposing parent insects to atmospheres in which continuous aerosol mists of cancer-causing chemical solutions were maintained.

He had his first success with a war gas that never saw action, one of the nitrogen mustards. When he found that this would produce both mutations and chromosomal rearrangements, he tried other cancer-causing chemicals, and found that he could produce mutations with four of them: dibenzanthracene, methylcholanthrene, benzpyrene and beta-naphthylamine. He tried 19 other chemicals that do not cause cancer in laboratory mice, and none of them produced mutations in his fruitflies. He regards the fact that mutations arise in response to treatment with cancer-causing chemicals, and to them only, as highly significant in its bearing on the mutation theory of cancer origin.

—From *Science News Letter*, May 10, 1947, p. 295.

*The development of new therapeutic agents has greatly improved the treatment of certain local infections which previously has been difficult. This article describes the successful use of penicillin in infections of the eye.*

## Current Status of Penicillin in Ocular Infections\*

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A summary of the history of penicillin<sup>1</sup> shows that Pasteur and Joubert in 1877 first observed that a substance produced by one organism was capable of arresting the growth of another.<sup>2</sup> In 1929 Fleming<sup>3</sup> noted the inhibition of growth in a colony of staphylococcus contaminated by mold, and found that the mold was a strong antibiotic, nontoxic to animals, and that it killed test-tube growth of many gram-positive bacteria. He named the substance penicillin. Florey<sup>4</sup> and co-workers were successful in 1938 in extracting penicillin. The first patient was treated February 12, 1941, with good response, but died when the supply of penicillin ran out. By June 1941 six patients with advanced septicemia had been treated intravenously, all responded, but two died when penicillin again gave out.<sup>5</sup>

The gram-positive streptococcus, staphylococcus, pneumococcus, *B. anthracis*, *Corynebacterium diphtheriae*, *Actinomyces bovis*, *Clostridium tetani*, *Cl. welchii*, and the gram-negative gonococcus and meningococcus are sensitive to penicillin. Only those diseases caused by the sensitive bacteria are cured by penicillin. The activity of the substance is maintained in serum, pus, and autolyzed body tissues;<sup>6</sup> leukocytes are unaffected. Most types of streptococci and pneumococci are extremely sensitive to penicillin. Plasma concentrations of 0.03 and 0.3 unit per cc. are required for the inhibition of most strains of streptococci and staphylococci respectively. However, we must remember that the in vitro test subjects the organism to constant antibiotic action, while in vivo the action is transient. Because penicillin is excreted rapidly and may be absent in the blood two hours after injection, therapy depends upon maintaining an adequate supply in the blood. In generalized infection intravenous or intramuscular therapy is indicated. In infections of the meninges<sup>6</sup> and vitreous, into which penetration is slow, local treatment is indicated.

Organisms develop resistance to penicillin when inadequately treated. Meningococci for instance, allowed to grow in the presence of 0.3 unit per cc. can acquire the ability to resist 41 units of penicillin per cc.

There are three common ways of administering penicillin,<sup>7</sup> topical, intramuscular and intravenous. The object is to bring the infection under control as quickly as possible. In serious infections, a massive dose of 25,000 to 50,000 units is given intramuscularly with sustaining dosage of 240,000 units intravenously daily, or 20,000 to 40,000 units every three to four hours intramuscularly. Topical application of an ointment containing 1,000 to 2,500 units per gram, or a solution containing 1,000 to 2,500 units per cc. may be applied to the eye and adnexa every three hours. If sensitization occurs treatment is discontinued.

Experimental work on rabbit's eyes shows that sensitive streptococci and staphylococci<sup>6</sup> in the aqueous may be inhibited by 0.019 and 0.15 unit per cc. of penicillin respectively. Methods of treatment have been developed to surpass these levels; by instilling drops of penicillin solution of higher concentration into the conjunctival sac of inflamed or abraded eyes,<sup>8</sup> subconjunctival injection, cotton packs, corneal baths, iontophoresis, and direct injection into the eye.

All of these methods of treatment have been tested experimentally against standard infections, produced by the injection of pathogenic bacteria into rabbit's eyes, and they are all effective to a certain degree, but corneal baths, iontophoresis and direct injection give the widest margin of safety.

The most frequent cause of exogenous intra-ocular infection is the pneumococcus. Injection of pneumococci into the anterior chamber of rabbit's eyes, causes an acute endophthalmitis, which is followed by phthisis bulbi in untreated eyes. This infection may be treated best by iontophoresis. This method produces a high concentration of penicillin in the aqueous which remains for four hours (19.2 units).

The second common cause of intra-ocular infection is the staphylococcus, and experimental endophthal-

\* From the Institute of Ophthalmology, Presbyterian Hospital, New York, N. Y.

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mitis produced in rabbit's eyes with these organisms, can be controlled by iontophoresis.

When the lens is deeply infected experimentally with pneumococci, staphylococci or *Clostridium welchii* an inflammation ensues which cannot be controlled by any instillation or any conservative topical procedure, it then becomes necessary to inject penicillin into the lens.

In infection of the vitreous of rabbit's eyes, produced by injections of penicillin-sensitive strains of bacteria, the treatment consists of an injection of 0.1 cc. of 100 to 250 units of penicillin solution directly through the sclera. This is followed by a high bacteriostatic level of penicillin in the vitreous which persists for 48 hours. At this time the concentration is still five times that required for protection.

When high concentrations of the common commercial penicillin product are injected experimentally into the vitreous atrophy of the retina may develop in areas, and repeated injections have deleterious effects.

The opportunity to investigate experimentally the action of penicillin on human eyes occurs occasionally. When it does occur it is not surprising to find that the dosage requirements are greatly increased. Von Sallmann<sup>8</sup> found that instillation of penicillin into the conjunctival sac of an abraded and inflamed eye resulted in values only one-fifth of that found in rabbit's eyes.

Experimental work on hopelessly blind human eyes was reported by Rycroft<sup>9</sup> who injected a solution containing 4,000 units per cc. subconjunctivally and found that penicillin reached the aqueous in 15 minutes. Assay showed the presence of penicillin in concentration above bacteriostatic requirements.

Von Sallmann,<sup>8</sup> working on human eyes destined for enucleation, found that cotton packs containing 20,000 units of penicillin per cc. when placed under the lids, produced about 2.3 units after one and a half hours and that the instillation of four drops of a solution containing 20,000 units of penicillin per cc. resulted in a concentration of 0.6 unit per cc. of penicillin in the aqueous.

In general the findings in experimental data have applicability to the human eye if the infections investigated are caused by susceptible organisms.

Clinical experience with penicillin in the treatment of most external disease infections has shown good results. Struble and Bellows<sup>10</sup> reported that satisfactory regression occurred in acute and chronic catarrhal conjunctivitis, and in one catarrhal marginal ulcer of the cornea, following the use of penicillin locally. They state that an enormous concentration of penicillin can be achieved in the conjunctiva following its local ap-

plication, a concentration which surpasses by far any secured by even the most massive intravenous dose.

Juler and Young<sup>11</sup> report on the successful treatment of 23 septic corneal ulcers by local applications of penicillin in solution and in crystal form.

Orbital cellulitis was treated by Sloane<sup>12</sup> by intravenous injections with good results.

Eighty-nine eye infections were treated by Florey and Mann.<sup>5</sup> The infections consisted of acute conjunctivitis with corneal ulcers, blepharitis, infected eye sockets, and one infected meibomian cyst. Included in the list were six cases of dacryocystitis. Blepharitis was treated by rubbing penicillin ointment containing 800 units per gram, into the lid margin with a glass rod, three times a day. All cases were free of pathogens after treatment. In treating dacryocystitis, the sac was washed with a solution of penicillin containing 800 units per cc. five times a week. Cultures became sterile, but the results were not good. One case of gonococcal ophthalmia neonatorum was treated by instilling a few drops of penicillin solution containing 1,200 units per cc. into the eye hourly.

Sorsby<sup>13</sup> reported good results in the treatment of ophthalmia neonatorum following the instillation of penicillin solution into the conjunctival sac every half hour, for three hours, then hourly for 24 hours. Recovery was secured in 21 out of 22 cases.

The prophylactic use of penicillin for ophthalmia neonatorum is not yet advisable, although the successful use of penicillin for this purpose has been reported. Prevention of congenital syphilis<sup>14</sup> by the prenatal use of penicillin is far better than the treatment of congenital syphilis. The administration of 2,400,000 units in seven and a half days in the third month, repeated in the seventh month of pregnancy seems most efficient. Interstitial keratitis has resisted treatment but may yield to massive doses of penicillin.

A few bacteria such as *B. pyocyaneus*, *Morax-Axenfeld diplobacillus*, *Haemophilus influenzae*, and *Friedlanders bacillus*, may be the cause of intra-ocular infections. They are only slightly sensitive to the antibiotic effect of penicillin, but they are susceptible to the action of the sulfonamides.

For early treatment a combination of penicillin and sulfonamides is favored in cases where the infecting agent is unknown. Sulfonamides do not exert a deleterious effect on penicillin activity *in vitro*.<sup>6</sup>

Several cases in which the combination of penicillin and sulfadiazine or sulfacetamide were used successfully, were recently reported by Dunnington and von Sallmann.<sup>15</sup> Two were cases of metastatic meningococcic endophthalmitis in children, one was a perforating injury of the cornea, two were postoperative



infections with beginning endophthalmitis, and one followed infection of a filtering cicatrix. The treatment in these cases was by local iontophoresis and intensive systemic sulfadiazine medication. In one case iontophoresis with penicillin and sulfacetamide was used with success.

Penicillin alone has been employed in intra-ocular infection with good results. Sanders<sup>16</sup> reports on an infected perforating corneal wound in which treatment was delayed for five days. He was unsuccessful with sulfadiazine used systematically, but noted a regression of inflammation following the use of intravenous penicillin, paracentesis, and local instillation of penicillin drops.

Another case of delayed treatment was reported by Metius<sup>17</sup> who treated a perforating injury of the cornea, five weeks and ten days after injury. This patient had been followed and treated, but the eye became painful and inflamed and many thick corneal precipitates appeared. Paracentesis with irrigation of the anterior chamber was done by means of a needle through which a solution of penicillin (0.25 cc. of a 250 unit per cc.) was injected. The eye was white at the first dressing 48 hours later.

Ingalls<sup>18</sup> treated a boy for a penetrating injury of the cornea, complicated by hypopyon, and secondary glaucoma following a traumatic cataract. A linear extraction was done 24 hours later. Substitution of a solution of penicillin for the usual saline irrigation was followed by a regression of the inflammatory signs.

Berke<sup>19</sup> treated a boy for a penetrating injury of the cornea near the limbus, which was accompanied by hypopyon and traumatic cataract. Following an iridectomy, he washed out the anterior chamber with a solution of penicillin and all inflammatory signs disappeared.

Successful treatment of an abscess in the vitreous<sup>20</sup> by the injection of penicillin through the sclera has been reported by Feigenbaum and Kornbluth.

### CONCLUSIONS

Since the appearance of the first crude extract, penicillin has proved itself effective against sensitive strains of pathogenic organisms. At first many of the gram-negative bacilli were considered insensitive to penicillin but as time goes on, and larger doses are employed, more bacteria are proving sensitive.

There are some strains of bacteria usually sensitive which seem to resist the action of penicillin. This may be due to built up resistance following inadequate treatment or the need of initial high dosage.

Early treatment of intra-ocular infections should not wait on laboratory findings but should be insti-

tuted immediately with combined penicillin and sulfonamide therapy.

Many cases of trauma to the anterior segment of the eye include wounds of the cornea and lens. Treatment of these infected cases by irrigation with penicillin solution is warranted.

In the presence of vitreous infection there should be no hesitancy in giving intravitreal injections of purified penicillin, since in most cases the eye is otherwise doomed.

### BIBLIOGRAPHY

1. Editorial: History of penicillin, *J. A. M. A.*, 126:170 (Sept. 16) 1944.
2. Compt. rend. Acad. d. sc., 85:101, 1877.
3. Fleming, A.: On the antibacterial action of cultures of a penicillium with special reference to their use in the isolation of *B. influenzae*, *Brit. J. Exper. Path.*, 10:226 (June) 1929.
4. Florey, H. W.: Penicillin: A survey, *Brit. M. J.*, 2:169 (Aug. 5) 1944.
5. Florey, M. E.: General and local administration of penicillin, *Lancet*, 1:387-396 (Mar. 27) 1943.
6. Rammelkamp, C. H., and C. S. Keefer: The absorption, excretion and distribution of penicillin, *J. Clin. Investigation*, 22:425-437 (May) 1943.
7. Leopold, I. H., and W. O. LeMotte, Jr.: Penetration of penicillin in rabbit eyes with normal inflamed and abraded corneas, *Arch. Ophth.*, 33:43 (Jan.) 1945.
8. von Sallmann, L.: Penetration of penicillin into the eye, *Arch. Ophth.*, 34:195-201 (Sept.) 1945.
9. Rycroft, B. W.: Sub-conjunctival penicillin and intra-ocular infection, *Brit. J. Ophth.*, 29:501-511 (Oct.) 1945.
10. Struble, G. C., and J. G. Bellows: Studies on the distribution of penicillin in the eye and its clinical application, *J. A. M. A.*, 125:685-690 (July 8) 1944.
11. Juler, F., and M. Y. Young: The treatment of septic ulcer of the cornea by local applications, *Brit. J. Ophth.*, 29:312-322, 1945.
12. Sloane, H. O.: Orbital cellulitis treated successfully with penicillin, *J. A. M. A.*, 126:164-166, 1944.
13. Sorsby, A., and E. Hoffa: Local penicillin therapy in ophthalmia neonatorum, *Brit. M. J.*, 1:114, 1945.
14. O'Leary, P. A., and R. R. Kierland: Today's treatment of syphilis, *J. A. M. A.*, 132:430-434 (Oct. 26) 1946.
15. Dunnington, J. H., and L. von Sallmann: Penicillin therapy in ophthalmology, *Arch. Ophth.*, 32:353-361 (Nov.) 1944.
16. Sanders, N. W.: Treatment of a perforating corneal wound with penicillin and sulfadiazine, *J. A. M. A.*, 127:397 (Feb. 17) 1945.
17. Mietus, C. A.: Ocular therapy with penicillin used topically, intra-ocularly and systemically with case reports, *Am. J. Ophth.*, 28:173-179, 1945.
18. Ingalls, R. G.: Penetrating wounds of the cornea with hypopyon treated with penicillin, *Am. J. Ophth.*, 29:1152 (Sept.) 1946.
19. Berke, R.: Personal communication.
20. Feigenbaum, A., and W. Kornbluth: Intravitreal injection of penicillin in a case of incipient abscess of the vitreous following extracapsular cataract extraction, *Ophthalmologica*, 110: (Nov.) 1945.

# WHAT'S YOUR DIAGNOSIS?

A 17-year-old white girl was admitted to the Medical Service on July 11, complaining of stiffness of the neck for three days.

She had been in excellent health until one week before admission when she developed constant aching pain in the right upper quadrant of the abdomen. Following the ingestion of some medicine that had been prescribed by her physician she developed a mild diarrhea which lasted for a few days. Four days before admission she developed a sore throat and nausea and vomiting that persisted for 24 hours. Three days before entry headache, pain and stiffness of the neck and left shoulder developed and became progressively worse. This was associated with a moderate fever (102°) but no chill. During the three days preceding admission she was unable to retain liquids, had difficulty in swallowing and regurgitated liquids through her nose. Large amounts of mucus accumulated in her throat and were expectorated with difficulty. Two days before admission she was quite weak and on the following day she was unable to move her left arm which was quite painful. The dysphagia increased and there was moderate impairment of speech. There was no respiratory distress nor mental changes. No sensory disturbances were noted and no pain of the extremities or back was present. Slight diplopia was noted on the day before admission.

Past history was not remarkable. There was no antecedent respiratory infection.

**Physical Examination.** T. 103°, R. 28, P. 120; B.P. was not recorded. She was well developed and nourished. She complained of headache and stiffness of the neck. Breathing was somewhat shallow and irregular but not labored. She cleared her throat frequently, producing small amounts of mucus. Skin was hot and dry. Head was normal. Pupils were normal and reacted physiologically. Extra-ocular movements were normal. Oculi fundi were normal. Nose was clear. Soft palate moved well. Gag reflex was diminished. Voice was a little husky. Neck was moderately stiff and considerably weaker than would be expected. Expansion of the chest was good. Ribs moved well bilaterally with no use of accessory muscles. Breasts were negative. Lungs were clear. Heart was not enlarged. Tachycardia was present, the rhythm was reg-

ular. Sounds were of good quality and no murmurs, rubs or thrills were heard or felt. Abdomen was flat with no palpable masses or organs. Slight tenderness on deep palpation in right upper quadrant was elicited. She was unable to move her left shoulder or elbow but the motion of the wrist and hand were good. Reflexes in the left arm were absent. Reflexes in the right arm were hypoactive and both legs were normal. Hoffman and Babinski were negative.

## LABORATORY DATA

Urine	July 12	July 13	July 15
Sp. Gr.	1.030	1.020	1.025
Reaction	Acid	Acid	Acid
Albumen	2+	2+	2+
Sugar	2+	Neg.	Neg.
Microscopic	Neg.	Neg.	Few WBC and few hyaline casts

Blood	July 12	July 13
RBC	5,200,000	
WBC	15,150	17,400
Hgb.	14.5	
Differential	Seg. 76%; Eos. 1; Lymph. 19; Mono. 4	
Sed. Rate		38 mm./hr.
PCV		45
Kahn		Negative

Stool (July 13) Negative for parasites and blood.

**Spinal Fluid (July 11)** Opening pressure was 180 to 190; dynamics were normal; 10 cc. clear colorless fluid were removed. There were 126 cells, 95 lymphocytes and 5% polys. The Pandy was 1+. Spinal fluid protein was 48 mg.%.  
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**Course in Hospital.** She went progressively downhill. On the day of admission the respirations became difficult and accessory muscles of respiration were used. Her temperature came down to 98.6° by the third hospital day. There was a persistent tachycardia with the pulse ranging around 110. Respirations ranged from 30 to 40 per minute during the first three days. Because of the increasing difficulty in respirations she was placed in a respirator on the third hospital day and a Levine tube was inserted. About 12 hours after this her temperature rose to 106° and the pulse rate rose to 160 per minute. Despite alcohol sponges and sulfathiazole her temperature and pulse remained high until she died of cardiac failure on the fifth hospital day.

For answer, please turn to page 694

# Cases from The Medical Grand Rounds of the Massachusetts General Hospital

Edited by LEWIS K. DAHL, M.D.

BOSTON, MASSACHUSETTS

## CASES 20 AND 21

### GASTRIC ULCERS

DR. F. DENNETTE ADAMS: We are departing somewhat from the usual scheme of things this morning, chiefly at the request of the House Staff. It seems that there is a good deal of uncertainty on the part of the Staff as to the proper methods of handling gastric ulcer and especially pre-pyloric ulcer. So the House Staff has rounded up people in special fields and we are going to turn them loose and see if the problem can be thrashed out to the satisfaction of all.

First, we shall have a very quick presentation of two cases, simply to serve as a basis for the take-off. Dr. Schaaf will present the first case and Dr. Mitchel will present the second case.

DR. ROYAL SCHAAF: Our first patient, Mr. H., No. 547622, was 54 years of age, and a former truck driver. He came to the Massachusetts General Hospital on October 9, 1946 with a history of eleven years of progressive, crippling, rheumatoid arthritis. He had been treated recently at the Boston City Hospital. At the time of admission there was no history, past or present, of any gastro-intestinal difficulties.

In January 1947, following three months of uneventful ward care, he had a two-day episode of vomiting, diarrhea and nausea. No diagnosis was made, no specific treatment was given, and the symptoms disappeared spontaneously.

Two weeks later, on routine examination the stools were guaiac positive, and one week later there were massive, tarry stools. A barium enema was negative. Proctoscopy was negative. A gastro-intestinal x-ray series was made. The first series was reported as showing no disease of the duodenum; however, there was a filling defect of the lesser curvature of the stomach. Two days later, a second gastro-intestinal series was made. At this time, a second examiner did the work and he mentioned nothing whatever about the lesser curvature ulcer, but he stated that there was a curling of the esophagus and a freely-moving foreign body within the stomach. The patient subsequently denied having ingested a foreign body.

Coincidentally, the patient began to make a complaint of epigastric distress for which he was placed on a bland diet, and the symptoms subsided. Ten days following the second gastro-intestinal series, a third was made by a third examiner. At this time, the first gastro-intestinal series was reviewed, and the first and third series clearly demonstrated a pre-pyloric ulcer. No definite tumor mass was made out. A fourth gastro-intestinal series was requested. This was performed, and again there was a report of ulcer, most probably in a tumor mass.

The x-ray department reviewed all films and felt justified in stating that the patient did have a tumor, and recommended operation. The Arthritic Service agreed that in view of the likelihood of carcinoma, the patient was in a sufficiently good state to be operated upon. He was transferred to Surgery and a subtotal gastrectomy was performed. Following the operation, the patient did poorly. On the sixth postoperative day, his abdomen was re-opened, at which time all layers except the skin were found to be dehiscd. General peritonitis was present. There was no leakage from the duodenal stump and the anastomosis was intact. There was a pancreatic spillage into the duodenal cavity.

The following day he expired.

At autopsy, in addition to the gastrectomy and rheumatoid arthritis, he was shown to have acute pancreatitis.

DR. ADAMS: What about the microscopic examination of the mass?

DR. SCHAAF: That was benign.

DR. ADAMS: Dr. Mitchel will now present his case.

DR. DUANE H. MITCHEL: Mr. B., No. 564863, a 52-year-old male, entered the hospital on March 12, 1947 on the Surgical Service, complaining of epigastric pain of three and a half years' duration. In 1945, during one bout of pain, his appendix was removed, without relief of symptoms. In March 1946 the symptoms became more severe, and were described at that time as nonradiating epigastric pain, occurring one and one-half hours after meals and during the night, and always relieved by food or soda.

At this time, x-rays that were taken in an outside hospital revealed an ulcer in the pre-pyloric region of the stomach. He was then placed on a soft diet, with frequent feedings, and during the course of one month, he was relieved of his symptoms. During the past year, on a fairly normal diet, he had had very few complaints, having pain only about once a week, which was relieved by the ingestion of food. However, during this time, he lost 15 pounds in weight.

On February 21st of 1947, without previous complaints, he suddenly had a massive hematemesis. He was taken to the same hospital where x-rays again revealed an ulcer similar in size and position to the earlier one. The bleeding ceased on conservative measures.

On admission to this hospital, the physical examination was entirely negative except that upon deep palpation of the abdomen there was tenderness in the left lower quadrant.

Laboratory studies revealed a normal differential; the urine was normal; stools were guaiac negative; hemoglobin was 13.0 Gm. Gastric analysis revealed five units of free acid and nine units of total acid. X-rays taken here revealed a normal stomach, except for a small hiatus hernia. The barium passed through the pylorus readily and revealed that the duodenal cap was normal in contour. However, there was a small defect in the pylorus. Because the pyloric canal was not well filled, it could not be determined whether the ulcer lay on the gastric or duodenal side. A verbal report from the Vincent Laboratory stated that smears of the gastric contents were positive for malignant cells.

A subtotal gastrectomy was performed on March 19th. The patient did well, until the tenth post-operative day, when loops of the small bowel were eviscerated necessitating resuture of the wound. This prolonged his hospital stay one week.

Pathologic report of the sections removed described an active ulcer 5 mm. in diameter, in the pylorus, in line with the lesser curvature of the stomach and extending slightly into the duodenum. There was a second ulcer, partially healed and somewhat smaller in size, a few mm. below it. There was no evidence of malignancy.

DR. ADAMS: Dr. Eyler of the x-ray department who has been reviewing these cases with Dr. Schatski, will discuss the subject from the x-ray standpoint.

DR. W. H. EYLER: The radiologists who have written about these ulcers have limited themselves to an area within one inch of the pylorus. At the Mayo Clinic, they limit it to three centimeters. We have taken as our definition of pre-pyloric ulcer one the center of which is an inch from the pylorus.

In reviewing these cases, we found, in the period from 1942 to 1946, 43 cases which have adequate x-ray examinations and clinical records. Of these, 25 were histologically benign, 18 were histologically malignant. Dr. Schatski has reviewed the films in these cases, without the aid of clinical history or fluoroscopic notes, and he thought that 5 out of 18 malignant lesions were grossly benign by x-ray. Of those which were histologically benign, there was one error in diagnosis, and there was one case in which the film did not permit a complete opinion to be expressed.

DR. ADAMS: Dr. Robbins, will you comment for us on this matter?

DR. LAURENCE L. ROBBINS: There are one or two points that are of importance. First of all, some of these lesions are particularly difficult to demonstrate, as the first case clearly showed. I didn't examine the patient at any time, but saw the films, and felt from what could be seen on the films that it probably was a tumor with an ulceration in the center of it. It was never possible to bring the lesion into profile. I was on exactly the same spot as the examiner who had seen the patient, because on none of the examinations was it possible to demonstrate the lesion adequately fluoroscopically. That, of course, hindered the examination considerably.

A second point is that in those lesions which fairly obviously are cancer, in other words would be clearly cancer as one examined the specimen, there should be very little difficulty in the x-ray diagnosis. Those which are grossly benign but turn out to be malignant histologically, are impossible to differentiate radiologically.

Third, it is often extremely difficult to be certain where exactly the crater is. If you can be certain that it is in the pre-pyloric area, then we, at least, believe that those findings which have pertained in the past to pre-pyloric ulcer must still be considered. Cases in which it is difficult to be certain that the pre-pyloric area is involved rather than the pylorus, become extremely difficult to analyze; it may require two or more examinations, with very thorough study, to be certain. Those lesions which lie in the pylorus or which lie on the stomach side of the midportion of the pylorus, are more likely to behave like pre-pyloric ulcers. Those that lie toward the duodenal side behave much more like duodenal ulcers.

DR. ADAMS: In recent months, it has become the procedure to send gastric fluid to the Vincent Laboratory for study in an effort to determine whether or not the diagnosis of malignant disease can be made by examination of the secretion. Miss Graham of the Vincent Laboratory is going to tell us what their findings have been to date.

MISS RUTH M. GRAHAM: To date, in the Vincent Laboratory, we have examined 49 cases for carcinoma cells in the aspirated gastric fluid. The method is very simple. It requires only a very fresh specimen, some of which is put on a slide, stained, and searched for the cancer cells.

Of these 49 cases which we have studied, there was carcinoma of the stomach in 24. We have diagnosed carcinoma in 15 of those, which gives an error of 37 per cent.

Of the negative cases, we have had 25, and we have incorrectly diagnosed one—the case presented here this morning. It might be interesting to know that of the 24 cases of carcinoma, four were operable, and in all of those four, we found carcinoma cells in the aspirated gastric fluid. Two of the cases were carcinoma *in situ*.

In all the methods for studying secretions by cytologic means, we have found that cells which can be recognized are more apt to desquamate in the early lesions than in the late lesions. This is probably due to the fact that in a long-standing tumor, there is necrosis at the surface and good, healthy, malignant cells that can be recognized are not shed.

DR. ADAMS: In these 24 cases of carcinoma which you diagnosed correctly . . .

MISS GRAHAM: We diagnosed 15 of the 24.

DR. ADAMS: In how many of those cases which you diagnosed correctly as showing malignancy was there some doubt as to whether the lesion was benign, as determined by other methods?

MISS GRAHAM: In three of them.

DR. ADAMS: The others were all thought to be carcinoma?

MISS GRAHAM: Yes. In three the x-ray diagnosis was benign ulcer; grossly, in two they were thought to be benign; only on section was it possible to tell.

DR. CHESTER M. JONES: It seems to me that you have a constantly desquamating surface in the stomach. Aspiration always shows a large number of cells. That must mean that there is a constant regeneration of cells. How difficult is it to differentiate between regenerating cells that are normal, that have been caught in the smear, and the carcinomatous cell? In other words, isn't it going to take a long experience before it is really possible to differentiate accurately between the two?

MISS GRAHAM: We have certain criteria that we use to distinguish a regenerating cell from the carcinoma cell. Certainly in the number of gastric cases that we have examined so far, the groups that we have seen have been typical as regards the differentiation of carcinoma. One will see, often, very active cells with active nuclei in the normal cells, and they may be

regenerating. The cytoplasm remains the same. In malignancy, they are distorted.

DR. ADAMS: In many of these cases gastroscopy is done, and the problem, of course, then becomes this: Can the gastroscopist determine which is malignant and which is operable?

Perhaps Dr. Benedict will give us some figures and facts.

DR. EDWARD B. BENEDICT: The value of the gastroscopy in the differential diagnosis of benign and malignant ulcer is chiefly in the demonstration of malignant ulcer. That is, if I find a lesion that is definitely nodular, and over which no peristalsis passes, and which is rigid and irregular, it makes me feel quite definitely that it is malignant. That bit of positive evidence is valuable.

We are hampered in gastroscopy by not being able to take a biopsy. Negative evidence is of very little value. I feel that we never can rule out histologic malignancy. I cannot understand in the first case presented why gastroscopy was not done. I think that the gastroscope is of particular use when the x-ray is doubtful. In that case, we had four different reports, by x-ray examination. There is no question but that the gastroscope is of a great deal of value, when it is positive; but when it is negative, or when the lesion is beyond the reach of the gastroscope, that is not of so much significance.\*

DR. MAURICE FREMONT-SMITH: Dr. Benedict, how far down can you usually see? Can you see the prepyloric area?

DR. BENEDICT: It is sometimes hard to see. We see the pylorus itself, in about half of the examinations. It is one of the difficult areas to visualize.

DR. WALTER BAUER: How about giving us a few figures?

DR. ADAMS: I was about to ask you how many times have you picked up a carcinoma that the x-ray department were not sure of or thought was benign?

DR. BENEDICT: I can't give you any figures on that.

DR. BAUER: We were hoping that everybody today would have exact figures.

DR. BENEDICT: Well, there have been enough of them, so that it is definitely worthwhile. This isn't x-ray versus gastroscopy. It is gastroscopy plus x-ray. That is, it is every method that may be used that can be helpful. I can think of a good many cases, where there has been a doubtful x-ray and we have come out pretty flat-footedly with a diagnosis of carcinoma.

DR. BAUER: How about the reverse?

\* *Editor's Note.* This patient was not examined by means of a gastroscope because of a rheumatoid deformity of the cervical spine.

DR. BENEDICT: If they are positive for carcinoma, I don't get to see the patient at all. What is the use? The x-ray comes first; everybody will admit that.

DR. JONES: Is it true that there is a group of cases in which you have seen a lesion, and the x-ray hasn't found it? And they have found lesions that you haven't been able to see?

DR. BENEDICT: Yes, that is true.

DR. JONES: So it has to be a supplemental affair. Each one supplements the other to fill in the total?

DR. BENEDICT: Well, I analyzed some 230 cases some time ago and found that if the gastroscopist actually got a good look at the lesion, the batting average was better than the x-ray in the differential diagnosis; but there are mechanical difficulties, such as hemorrhage, difficult patients, spasm, angles, J-shaped stomachs, etc.

DR. JONES: Isn't it worthwhile pointing out, too, that within a few years, Schindler maintained that he could always tell cancer of the stomach, when seen with a gastroscope? That is certainly not true.

DR. BENEDICT: He doesn't maintain that any more. But I think it is true that the gastroscopist sees living stomachs and he can tell a little more than the pathologist can from the gross appearance of the stomach after death.

DR. BAUER: What can you tell?

DR. BENEDICT: I think the presence of the circulating blood in the living tissues is important. You can see nodularity and irregularity that fade out almost immediately after resection or death, also rigidity and lack of peristalsis.

DR. BENJAMIN CASTLEMAN: I should agree to that.

DR. ADAMS: Dr. Claude Welch, as we all know, has been studying this cancer-ulcer problem for a number of years. He and Dr. Allen have written a number of papers on the subject. We asked Dr. Welch to come over here and state his views, and I might say that he, also, has been harassed by a series of specific questions which the House Staff doctored up for him. He will first, I hope, discuss the situation generally, and then go ahead and answer the questions. Dr. Welch.

DR. CLAUDE WELCH: I feel somewhat like a sheep in the woods, over here this morning: I guess my only comfort is that you probably are all armed with stethoscopes instead of scalpels!

I was handed this list of searching questions by Dr. Dahl a couple of weeks ago. Then the request was also made that I be as quantitative as possible. So if I bore you with statistics, don't consider me entirely to blame. I thought we would first go over the series of problems in general terms, and then come back to the specific questions. You will find the talk will cover most of the points you are wondering about.

Of course, this whole ulcer-cancer problem is a troublesome one, especially in the pre-pyloric region. Our attention was drawn to it in 1940 when we received several patients who had spent a year and a half or two years under medical therapy before subjecting themselves to surgery, for what was obviously pre-pyloric cancer. It, therefore, seemed well to go over the whole problem again.

We attempted to prove the following statements:

1. Gastric ulcer cannot be distinguished from cancer in a high percentage of cases.

2. Gastric cancers that simulate ulcer comprise an especially favorable group for cure. On this basis alone, surgery should be the treatment of choice for gastric ulcer.

3. End results appear to substantiate the effectiveness of subtotal gastrectomy for gastric ulcer.

In order to prove these statements, we reviewed the records of all the patients who entered the hospital with a diagnosis of gastric ulcer between 1930 and 1940. (Table 1.) There were 277 of these patients.

TABLE 1  
*Gastric Ulcer*  
*Error in Diagnosis of Cancer*

	NUMBER OF CASES	PER CENT
A. Entire group		
Original diagnosis ulcer	277	
Final diagnosis cancer	39	14
B. Patients treated medically*		
Original diagnosis ulcer	175	
Final diagnosis cancer	13	7.4
C. Patients treated by gastro-enterostomy		
Postoperative diagnosis ulcer	23	
Cancer proved by follow-up studies	4	17
D. Patients treated by resection*		
Preoperative diagnosis ulcer	69	
Cancer proved histologically	30	43

\* Several patients are included in both groups B and D.

They were followed in an attempt to determine the final diagnosis. Out of the final number of cases with an original diagnosis of gastric ulcer (277), 39 had cancer, an error of 14 per cent in the entire survey. This error struck us as astonishingly high, and so we were interested to find that the error in most other clinics has been approximately the same. For example, at the Mayo Clinic, figures show between 10 and 20 per cent error.

This table includes the entire group of 277 patients; as you see, there was a 14 per cent error in diagnosis. Group B shows the number of patients treated medically. I don't mean that they were treated ten days or two weeks. They were followed for a period of over two months, with an average length of time of

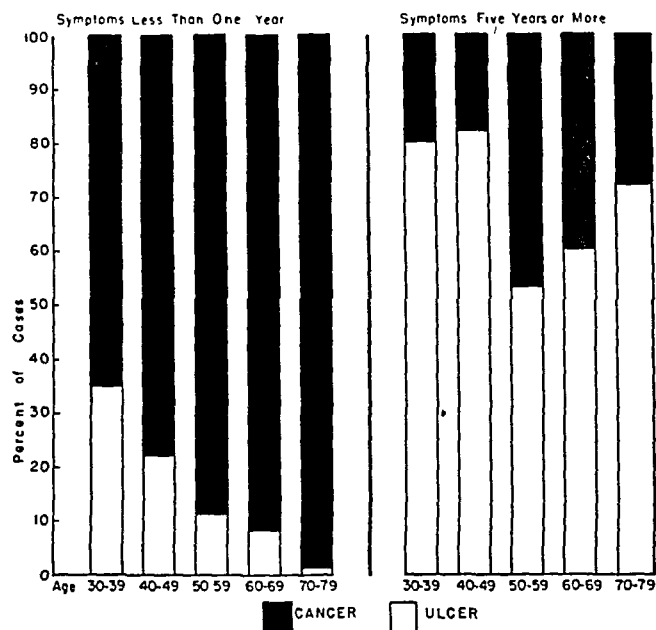
COMPARISON AGE AND DURATION OF SYMPTOMS  
GASTRIC ULCER & CANCER

FIGURE 1 \*

14 months, before being subjected to surgery. In other words, the original diagnosis was ulcer, in 175 cases, and there was a final diagnosis of cancer in 13 of these cases, or an error of 7.4 per cent.

Now what did the surgeon do during the same time? He received some patients and, thinking that the diagnosis was ulcer, performed gastro-enterostomy. Of this group of 23 with the diagnosis of ulcer, cancer was proved by follow-up studies in 4 or 17 per cent.

The next group of 69 patients was treated by resection with a preoperative diagnosis of ulcer. Cancer was proved histologically in 30 or 43 per cent.

But, primarily, we are interested in the next question. Is there any way to differentiate the patients with ulcer from those with cancer? We went over all the possible methods. With the exception of the cytologic diagnosis from gastric washings recently developed, we took into consideration the following factors: the age of the patients and the duration of symptoms, the location of the lesion, the size of the ulceration, the hydrochloric acid level of the gastric contents, the rate of healing under medical therapy, and the type of pain. We analyzed each one of these factors in an attempt to see what we could make out of them.

As to the age and duration of symptoms, the patients who are in the older age groups with lesions of short duration are more likely to have cancer than

to have ulcer. On the other hand, patients who have symptoms of a longer duration are more likely to have ulcer than cancer (Fig. 1).

Much more important than this factor is the one that has to do with the location of the lesion. In Figure 2 the stomach is divided into different areas. As you know, the work of Hampton, many years ago, indicated that the incidence of carcinoma was 90-100 per cent in the pre-pyloric area. As time went on, this percentage has been cut down progressively.

During this period, of all the ulcerating lesions located in the pre-pyloric area, 65 per cent were cancers. Obviously, a good x-ray man is sure that many are cancer rather than ulcer. So the questionable cases will be 12 and 15 per cent as Drs. Schatski and Eyer have shown.

Figure 3 refers to the size of the ulcers. The larger the ulcer, the higher the chances are of cancer. As to the gastric analysis, the only thing that we regard

## APPROXIMATE INCIDENCE OF CANCER IN GASTRIC ULCERATION

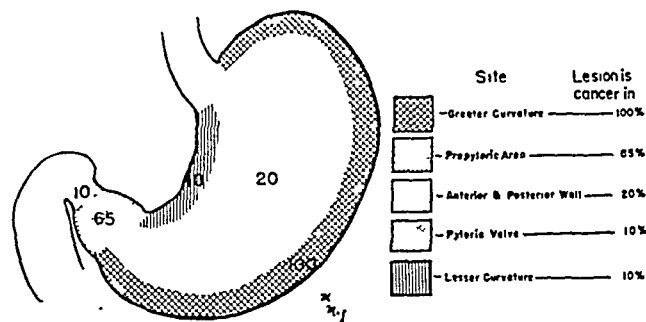


FIGURE 2

of importance is the presence or absence of free hydrochloric acid (Figure 4). If one considers gastric cancer, about one-third of the patients will have free hydrochloric acid present. In the group we are discussing, the ulcer-cancer group, the percentage of hydrochloric acid is the same as in the benign ulcers.

Now as to the rate of healing of ulcers. I am showing a patient's film because it is rather interesting. This man had been followed in the OPD for a year when he came into the hospital for his ulcerating lesion of the lesser curvature in March 1939. He was in the hospital, had careful medical treatment, with gastroscopy and x-ray studies, and by April 1940 the ulcer had changed so that it was regarded as healed by the x-ray department as well as by the gastroscopist. He was sent back to the outpatient department. Three months after that a gastro-intestinal series showed a lesion at exactly the same spot. He had a gastric resection at that time, and carcinoma was found. This represents one of the few cases of carci-

\* This and the following diagrams first appeared in the ANNALS OF SURGERY, Vol. 114 (Oct.) 1941.

noma that seems to have healed by all known methods of observation that are available.

We believe that immediate surgery is indicated:

1. If the ulcer is of short duration and the patient is over 50 years of age.

2. If the ulcer is over 2.5 centimeters in diameter.

3. If there is no free hydrochloric acid in the stomach.

4. If the ulcer is on the greater curvature or in the pre-pyloric area.

5. If the ulcer is chronic and on the lesser curvature.

Other patients with gastric ulcer require hospital observation, and surgery if healing is not complete within a month.

Now we must make a transition because of the questions asked me. Suppose patients have gastric resection; how uncomfortable are they from the so-called postgastrectomy syndrome? In answer to that prob-

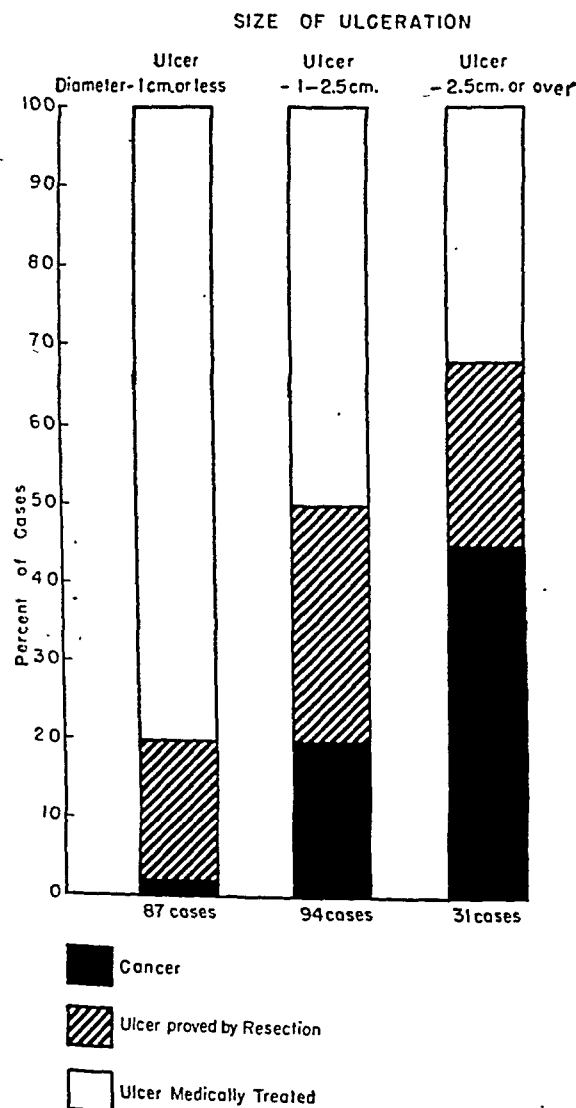


FIGURE 3

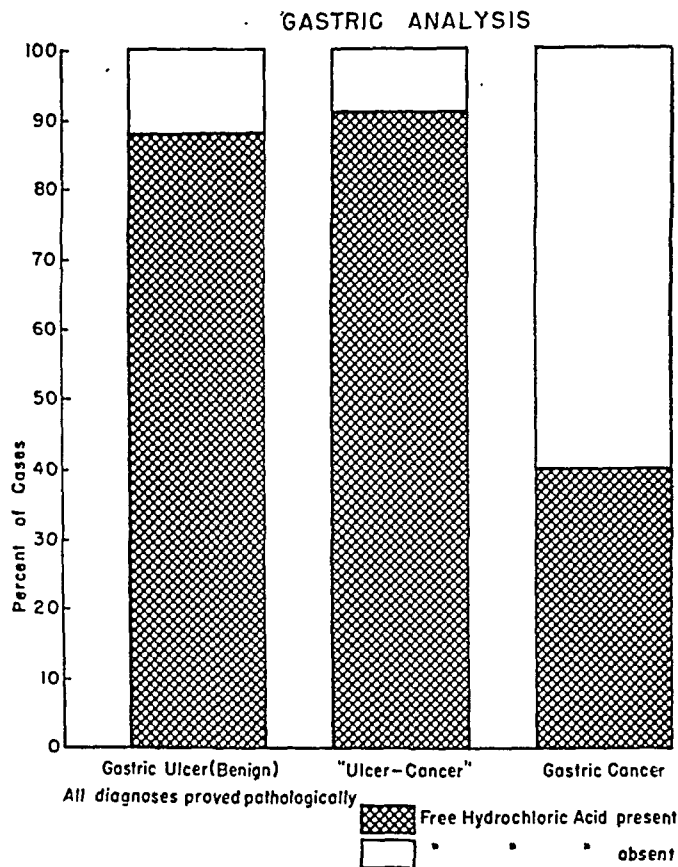


FIGURE 4

lem, we have to consider a different group of cases. The postgastrectomy syndrome is rarer after a gastric resection for gastric than for duodenal ulcer; that is a well-known fact and has been proved by several follow-up studies. These next tables deal with resections for duodenal ulcer, which is the worse group, and are based on a group of private patients who were followed accurately. We studied 129 cases operated upon five to fifteen years before, to find out their symptoms. Of this group, a little over two-thirds were entirely asymptomatic; 18 per cent had trivial symptoms. As an example of the trivial, one woman came in and said that she couldn't eat chocolate ice cream sodas after the operation. There were also such idiosyncrasies as a patient who could not take milk but could take anything else. The asymptomatic and those who had trivial symptoms were grouped together as excellent results, 87 per cent of the total. There was a satisfactory result in six per cent of the cases and a poor result in seven per cent.

What are the symptoms present? They are shown in Table 2. We have grouped the patients who have had excellent and who have had satisfactory results. A good-sized group of patients had symptoms that were referable to a small stomach; some had symptoms that were referable to a rapid emptying of the stom-



TABLE 2

*Duodenal Ulcer—Primary Resections*  
*Analysis of Excellent and Satisfactory Results*  
*Postoperative Symptoms*

Symptoms referable to a small stomach	24
Symptoms referable to rapid emptying of stomach	15
Symptoms of weight loss or inability to gain	5
Symptoms of secondary anemia	2
Symptoms of hypoglycemia	2
Special food intolerance	22
	—
Total symptoms	70
Total patients with symptoms	31
Average number symptoms per patient	2+

ach. Some had symptoms of loss of weight, of inability to gain. Others had symptoms of special food intolerances.

The symptoms referable to a small stomach can be subdivided into the inability to eat a full meal, or loss of appetite. Occasionally, there is nausea after eating, discomfort, or gas after eating; or, rarely, vomiting.

The special food idiosyncrasies are of considerable importance to you from a dietary point of view (Table 3). There were 22 patients with special food intolerances. A high place in this respect was taken by fats; carbohydrates were next, then milk, cheese, and chocolate, cabbage, spaghetti, coffee, hot drinks, and cold drinks.

It is interesting to observe that no patient had trouble with proteins but fats were frequent offenders. Obviously the postoperative symptoms can be improved by a change in diet.

Now, what are the poor results? There were nine of them: Three had anastomotic ulcers, three had postoperative hemorrhages, and three had severe post-resection symptoms.

The last problem concerns the mortality rates with gastric ulcer. The operative mortality will be around two per cent for any large series of patients.

Again, let me bring up the question: Suppose the patients have cancer, how are they going to get along? I shall not go into this very minutely with you, but out of every 100 cases of cancer of the stomach that

TABLE 3

*Duodenal Ulcer—Primary Resections*  
*Analysis of Results*

POSTOPERATIVE SYMPTOMS	
Intolerance to fats	5
Intolerance to carbohydrates	4
Intolerance to milk	3
Intolerance to cheese	2
Intolerance to chocolate, cabbage, spaghetti, coffee, hot drinks, cold drinks—1 each	8
	—
Total patients with special food intolerance	22

come into the hospital now, we can expect seven of them to survive for five years, regardless of the fact that we are resecting nearly half of the stomachs. Cancer of the stomach is a deadly disease, and rapidly so.

May I read specific questions that were asked me?

1. What is the incidence of ultimate malignancy of pre-pyloric lesions in those which cannot be proved to be malignant preoperatively with reasonable assurance by the usual methods of gastric x-rays, gastric washings, gastroscopy, etc.?

The answer to that, from the discussion you have heard this morning is somewhere in the vicinity of 10 to 15 per cent.

2. Does the incidence of malignancy in pre-pyloric lesions vary with increasing age?

The answer is "yes" as you can see from the table of incidence of the gastric ulcer and cancer.

3. What is the operative mortality by decades in subtotal gastrectomy?

Much more important than the age of the patient is the year in which the patient was operated upon. For instance, in 1930, he had about a 15 per cent chance of dying from the operation. But, if the operation were done in 1945 or thereafter, his chances of survival have been tremendously increased so that the mortality is now about 2 per cent.

4. What is the survival rate by decades of proved gastric carcinoma with and without operation?

All patients with cancer of the stomach die very fast, and a 35-year-old is as badly off as a patient of 80. Dr. Nathanson and I found that 50 per cent of the untreated patients were dead in a year and 75 per cent in 18 months.

5. Is there a difference in No. 4 between the minimal equivocal cases and the obvious cancers, both referring to the preoperative diagnostic status?

The answer is "yes." The curability rate after resection is roughly twice as great in the "ulcer-cancer" group as in the group with obvious cancer.

6. The incidence of distress and the approximate severity after a subtotal gastrectomy not in reference to the immediate postoperative period.

The answer to this question has appeared in the previous discussion.

DR. ADAMS: Thank you very much, Dr. Welch. Dr. Jones, would you care to add to the discussion?

DR. JONES: I don't think that much can be added to what Dr. Welch has said. In the main, I would be in complete accord. It seems to me that the risk of gastric cancer in the presence of a frank ulceration of the stomach is very great. I am sure that if we avoid ulcer located in the middle of the lesser curvature for an instant, there is no reasonable doubt that the in-

cidence of malignant lesions in the pre-pyloric area and of the greater curvature is so high and the dangers of surgery are so low relatively, that one has to choose in favor of surgery in almost every instance. There are cases where, because of the fact that the patient may be an undesirable risk, it is wise to try to be conservative, but not, obviously, in a case that is frankly carcinomatous. In pre-pyloric ulcer, in most instances, I would have no hesitation at all in asking for surgical intervention. We have a few patients that have been carried medically, even with a pre-pyloric lesion, but there have been good reasons for so doing. As a rule, it is bad judgment to do so.

What Dr. Robbins pointed out is pertinent; even the surgeons themselves cannot always identify the pylorus, so that certainly the x-ray man cannot. Therefore, the exact statement of where the ulcer is, isn't easy. But, if the x-ray localization is frankly pre-pyloric, then one has a right to be radical.

Just what incidence of malignant changes obtains in the group of pre-pyloric lesions is still a question. If you take Hampton's figures, reported in 1933, they were higher than those accepted at the present time. The present figures, just cited by Dr. Eyler, were approximately 42 per cent. Sosman's figures, obtained a short time after Hampton's study, were initially much lower, but gradually rose, until they were as high as 60 per cent or more, and Dr. Hampton's figures were dropping. Regardless of what figures you take, the incidence is so high in the particular group that they over-balance any risk or danger you assume from the point of view of surgical interference.

There is one thing that I think we have got to be quite aware of, and that is, that in this hospital or in any teaching hospital or any well-staffed, general hospital, where men are trained to do extremely skillful gastric surgery, the risk is relatively small, and it is smaller than the risk of waiting to see what is going to happen to a questionable lesion in the stomach.

That does not obtain, however, when you go outside, into many of the smaller community hospitals. Therefore, Dr. Welch's figures do not obtain at all, from the point of view of surgical risk, when the risk is assumed by untrained surgeons. That should be strongly stressed. Wouldn't you agree, Dr. Welch?

DR. WELCH: Yes.

DR. JONES: As to the criteria for surgical intervention, it seems to me that Dr. Welch has outlined those, by and large, very, very fairly indeed. The one exception I would like to make would be the question of the time involved in the healing of the lesser curvature ulcer. He didn't differentiate between the younger and the older age groups. I am certain that in my experience, with the older age group, those over

60, it takes a good deal longer to heal a benign lesion than in a youngster. Dr. Allen and I sat in on a case and finally treated it conservatively, in which it took a month and a half or two months of careful treatment to heal up the lesion completely. In a sense, Dr. Welch was talking about the over-all picture, which overlooks the individual case; yet almost all of the decisions are made in regard to a given case.

All cases of ulcer of the lesser curvature can be followed early, with gastroscopy and x-ray, and I think it is possible to say that a reasonable number of such patients should not be operated upon. Such a decision involves a full determination to follow the patient very closely and not let up on the follow-up at all. If one isn't prepared to follow up, one has no right to refuse surgery.

As to the symptomatology after resection, I am in complete discord with Dr. Welch. He interjected the surgery of benign and duodenal ulcers into the discussion where, in a sense, they had no place. When you talk about a benign lesion and the effects of subtotal resection, I am sure there are grounds for differences of opinion; let us put it that way. One of them is the question of postoperative endurance, the regaining of weight, and strength, apart from other more trivial symptoms.

We have just gone over the figures of well over 100 subtotal gastrectomies for benign lesions. Most of them were for duodenal ulcer. There probably was a third of that group which could be classified as having been underweight at the time of operation and never regaining weight, or, being underweight at operation and becoming still further underweight after surgery. That group hasn't done well. The ulcer hasn't come back; therefore, the reason for operation was fulfilled. But, on the other hand, they are not well people and they are invalided. The reason for this disability is not entirely clear, but we are very certain from what we think are careful metabolic studies that there is a tremendous loss of caloric material in the stools in a high percentage of these cases. We have found, for instance, as high as 45 per cent fat content, dried weight or 16 per cent of ingested fat lost daily in the stools of some of these patients and that is a high loss. The nitrogen loss is also much greater than that ordinarily found. One expects to find a gram and a half of nitrogen in the normal stool, day in and day out. We have obtained up to three grams, which is an appreciable loss. We think that from the figures coming through now, there may be carbohydrate loss as well. In other words, there is a failure of absorption. It is important to find a final explanation for these facts.

It is true that the majority of patients do well; but

15 per cent of the patients are seriously bothered and incapacitated. We must now try to see how closely we can get together, and to determine the reasons for our differences.

When it comes to cancer, it seems to me that disability from the operation is of no consequence whatever. I would agree with practically everything Dr. Welch has said, except that I think the lesser curvature lesion still can be regarded as one for individual decision, rather than for a blanket decision.

## CASE 22

### POSTERIOR PENETRATING DUODENAL ULCER WITH HEMORRHAGE

DR. WYMAN RICHARDSON: I want to bring up for discussion a patient with peptic ulcer, largely in order to discuss therapy.

Will you present this case, Dr. Bliss?

DR. HARRY A. BLISS: Mr. K., No. 185384, is a 50-year-old Irish night watchman, the father of five. Some ten years ago he began to have epigastric burning and distress about an hour and a half to two hours after meals. This has always been relieved easily by food, milk, or soda. These pains have persisted intermittently since that time. About two years ago he was seen in our Outpatient Department, where a hypertension of 210/100 was found. That, too, has persisted.

He had been well until about a week before admission. At that time he began to notice that he was light headed and moderately dizzy when he stood up. He also began to experience easy fatigue and typical anginal pain. This, in fact, was his presenting complaint. There was no vomiting, although he had had very black, tarry stools for six days prior to admission.

When he entered the hospital on March 11, 1947, he was seen to be a very pale man, with no evidence of shock. His blood pressure, in contrast to his previous levels, was 158/90. His pulse was slow. His heart was enlarged to the left, and there was a grade 2 aortic systolic murmur and a high-pitched, early diastolic murmur in the fifth interspace at the left sternal border. His abdomen was entirely normal, as was the remainder of the physical examination. His red blood cell count on admission was 2.0 million, with a hemoglobin of 5 Gm. A gastro-intestinal series made at the time of admission showed no ulcer, although one a week later showed a crater 0.5 cm. in diameter on the posterior wall of the duodenum. He has been very well since he has been in the hospital. He has had two blood transfusions, has been on a bland diet, with iron. His hemoglobin is 12 Gm. and red blood cell count about 4.0 million.

DR. RICHARDSON: I was about as wrong concerning this patient as I could be. In the first place, I said that heartburn is a relatively uncommon symptom in peptic ulcer unless there is considerable gastritis present. Since I made that statement, every patient with ulcer that we have seen, it seems to me, has complained of heartburn. How do you feel about that, Dr. Jones?

DR. CHESTER M. JONES: I think you were wrong.

DR. RICHARDSON: I think so too. The next thing was that here was a man with a loud aortic diastolic murmur with a relatively minor systolic component, and in the neck on the right side, there was a very loud to-and-fro murmur. I said that this man undoubtedly had serious aortic disease. I had heard aortic diastolic murmurs that were "hemic" murmurs, but I didn't think this was one because the systolic component was so slight. However, as his general condition improved, the murmur became fainter and fainter, until now nobody can hear it. I have not heard it for over a week, perhaps ten days. We are now calling it a hemic murmur.

DR. PAUL D. WHITE: Has the heart size changed, do you know?

DR. RICHARDSON: It was big. I don't know if we have checked it by x-ray recently. Have we, Dr. Bliss?

DR. BLISS: We checked it just once, when he entered. We have not had a second check.

DR. ROBERT S. PALMER: We recently have seen a patient with very severe hypertension and quite a wide pulse pressure, but still a high diastolic, 250/140. After her second sympathectomy it was noticed that the aorta, which had bulged to the left, appeared to shrink and to move back close to the spine in its usual position. Three days after operation, due to changes in the chest, probably pneumothorax and collapse, her pressure was very low indeed, being 100. Then, and even after her blood pressure recovered to a reasonable level, 130/90, the very marked aortic diastolic which she did have disappeared. Whether that is due to any change in the dilatation of the aortic ring or whether that is temporary with shock, we don't know. Subsequently with further rise of blood pressure, the aortic diastolic murmur again was apparent although less than before sympathectomy.

DR. WHITE: I think it is more common in anemia cases to have a mitral diastolic murmur than aortic diastolic, but you can have both in the same case.

DR. RICHARDSON: Have you heard aortic diastolic murmurs without a mitral component? That is what bothered me.

DR. WHITE: Oh, I think so, yes.

DR. BERNARD M. JACOBSON: May I add to the list a pulmonic diastolic?

DR. WHITE: I don't recall having seen it.

DR. EDWARD F. BLAND: We have had one severe anemia with red count below normal who had a very faint diastolic murmur along the left sternal border; it could have been either, but it promptly disappeared with treatment for pernicious anemia.

DR. RICHARDSON: We will accept this as a hemic aortic diastolic murmur. I would like to go on now to the question of therapy. The immediate therapy was obvious. This man was in moderate shock from hemorrhage and he received a number of transfusions, which, I believe, was absolutely correct treatment. I am not sure whether we always give enough transfusions at this point. We thought his bleeding stopped promptly. That brings up another point, namely, how long do stools remain guaiac positive after a single hemorrhage? I think many of us do not realize that the stool may remain positive following a single hemorrhage for as long as 14 days. Experiments were done with a single ingestion of 75 cc. of blood through a tube, and in some individuals the stool remained guaiac positive for as long as 14 days. This, of course, is particularly true if there is a sluggishness in moving the bowels.

A week ago we discussed the question of whether to give these patients transfusions in order to build their blood up to normal. I have expressed the opinion that that is not the best therapy for the following reasons: In the first place, there is a danger in giving blood, because there may be some error, a mixup of names, and whatnot, and you actually may have a fatal transfusion reaction. This doesn't happen very often, but when it does, it is awfully fatal.

The second point, which we discussed last week, is the possibility of transmitting homologous serum hepatitis, or syphilis, or malaria.

A third reason for not giving transfusions is that the blood you give is not freshly made blood, like that which the patient is making. Bank blood is, say, four or five days old. Assuming that the maximum life of a red cell is 90 days, the mean life of the cells given would be 45 days, if my mathematics is correct. In addition to that, the cells in bank blood probably are not as viable as the cells that an individual would normally make, so they do not stand up so well. I am quite sure of that. Then there is some fairly good evidence that transfusion may inhibit a marrow response. We know that bleeding, the loss of blood, is one of the greatest stimuli to marrow response; that is, the production by the marrow of a flood of new red cells. The reverse seems to be true also, that repeated transfusion tends to inhibit the marrow response. This is not according to the old ideas we had in regard to transfusion, but there is

some reasonably good evidence, both theoretical and clinical, to support this view. Finally, transfusion is an expense to the patient, at least for a bank charge, even if he does not buy the blood. It means in any case extra work for many people.

What, then, might be the reasons for giving transfusions? The first is that here is this patient, now in the hospital, not ready for what we think is the best therapeutic procedure. He must wait two weeks to build up his own blood, which has already reached a level of about 10 Gm., and is coming up rapidly. We could give him three transfusions, bring his blood up to normal, and have him operated on right way. That might save him a certain amount of expense, at least if we keep him in the hospital until his blood returns to normal, and also would shorten the time during which he might have a recurrence of his bleeding. Or else we can send him home and bring him back for surgery. This is what we plan to do. I am sure that one does not need to give these patients blood in order to restore their blood to normal. I say again that I think blood should be used freely to combat the shock of acute massive blood loss.

Now, in regard to the long range treatment. Here is a man of 54, with hypertension, with some suggestion of arteriosclerosis, with a large duodenal ulcer on the posterior wall, who has had a massive hemorrhage. I think that if we are ever going to decide this question on the basis of any kind of statistical set-up, this man surely falls into the group which should have a gastric resection, with the idea that this procedure will be less risky than to allow him to go out and have another hemorrhage, the next one very likely fatal. Our plan in regard to this patient is to have him operated when his blood returns to near normal, which will be in about two weeks. Dr. Jones, would you like to comment?

DR. JONES: I would be in agreement.

DR. RICHARDSON: Any discussion? Dr. Means? Dr. Aub?

DR. JOSEPH C. AUB: I would like to comment on the remarks you made about transfusion, by saying that a man like this loses much iron. Our war work showed that even if you do give blood cells which are 45 days old or give an inadequate transmission, so that practically all the blood given breaks up, the iron which you put into that man is incorporated into new cells—75 per cent of it within a week. So what you are doing, if you are not doing anything else, is giving him some hemoglobin for quick use, which is certainly worth doing.

DR. RICHARDSON: You can give him iron without giving it to him in the form of blood, if you wish. Here is a man who has had a single hemorrhage; his

iron reserves are presumably normal. He has plenty of iron.

DR. AUB: Well, if he has, that is all right.

DR. RICHARDSON: His blood is coming up very rapidly now.

DR. AUB: I was not referring to this man in particular, but one of the advantages of transfusion is that you are giving very readily available iron for a person to use even if the blood you give is not very good.

DR. RICHARDSON: Yes. That is a very good point. I did not mean to overlook it when you spoke of it. Whether or not the blood is destroyed, you are giving him hemoglobin, which will be re-used, or re-synthesized, if the blood is broken up.

DR. JONES: There is another point in which I think I might vary with you just a little bit, and that is in regard to the older age group, 65, 70, 75. If patients of this age have a major hemorrhage, in addition to care of shock, which is obviously urgent and necessary, it seems to me that they may do better if you carry them a little beyond the shock level with additional transfusions. I do not mean to bring them up to a normal hemoglobin, but I think an older person does not tolerate low hemoglobin levels, even if they are outside of shock level, as well as the younger person. I have the impression that they do better if you go a little bit beyond what you would do in a younger person. Have you any reaction to that?

DR. RICHARDSON: I agree with you.

DR. PERRY J. CULVER: It seems to me that there is another point to emphasize in deciding the time for operation following hemorrhage. Even though you do get the hemoglobin built up, these people have probably depleted their protein stores because of inadequate diet prior to bleeding. It would seem to me that you would have to allow an optimum time to provide replacement of lost protein with adequate diet before surgery, because you are going to have a negative nitrogen balance postoperatively. You would want to wait three or four weeks following hemorrhage before surgery, unless the risk of repeated hemorrhage is too great.

DR. RICHARDSON: I agree with you. It will be four weeks, if we wait another two.

A PHYSICIAN: I wonder if you would consider vagotomy?

DR. RICHARDSON: I am not an expert on the indications for vagotomy. Dr. Jones will check me on this, but at the present time I don't feel that vagotomy is a sufficient guarantee against recurrence of hemorrhage, and I would prefer to use it in the cases with intractable pain or in those cases with stomal ulcer. As a matter of fact, we were going to show a patient

with stomal ulcer this morning, but the surgeons got him up to the operating room before we could get him down here. He is having a vagal resection. Would you care to comment, Dr. Jones?

DR. JONES: Yes, I think probably you are right. I think these patients who have massive bleeding tend to bleed subsequently even when proper ulcer surgery is performed. Even the subtotal gastrectomy patients have a higher incidence of recurrent bleeding after the operation than, let us say, in the nonbleeding cases. We are beginning, several of us, at least, to feel that even with vagus resection the same thing may be true—that an uncomplicated ulcer will do much better than one which has bled previously. I think that is something which has to be observed over a long period of time. We now have an appreciable number of patients who have had a subtotal gastrectomy, followed by bleeding subsequent to operation. The recurrence of ulcer after subtotal gastrectomy is somewhere around 5 to 9 per cent. I don't know the recurrence rate after vagus resection. We do know ulcers have recurred. We have had one here out of 85 and they have had several in Chicago, and so forth. This point is still under observation, and I think we must go slowly.

This patient has had a major hemorrhage and it may well recur. The mechanism of gastric secretion will not be touched in one sense by vagus resection and by that I mean that gastric secretion in about six months' time probably comes back to almost the figure it was before, except for the psychic phase. Motility probably does much the same thing. If that is true, then other factors than psychic may cause ulceration, with further bleeding. So I think we have to put a question mark in front of vagus resection now.

#### *Editor's Follow-up Note*

This patient was discharged on the day of his presentation at Grand Rounds and was re-admitted to the East Surgical Service two weeks later on the 10th of April. On the 21st of April a subtotal gastrectomy was done without event. His postoperative course was uneventful and he was discharged on the 5th of May on a six meal bland diet. When he was seen in the Gastro-intestinal Clinic on the 3rd of June he had lost eight pounds over his discharge weight, complained of mild nausea at times after eating, was still on the six meal bland diet but was desirous of eating more meat in particular. He was given a high caloric, high protein, moderate fat diet—a modified six meal bland diet—and was to be followed in the Gastro-intestinal Clinic.

Answer to Quiz Case (p. 683): Anterior poliomyelitis

